THE American Journal OF Gastroenterology

VOL. 32, NO. 4 OCTOBER, 1959

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1. Hufford, A. R.: Rev. of Gastroenterology 18:588.

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VOL. 32, No. 4 OCTOBER, 1959

THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

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Abstracted from The American Journal of Gastroenterology, Vol. 30, No. 6, Dec. 1958

COMBINED DRUG THERAPY IN GASTROINTESTINAL DISTURBANCES

INCREASED BENEFIT THROUGH DIMINISHED SIDE REACTIONS

JOSEPH BANDES, M. D.

New York, N. Y.

"In the course of treating gastrointestinal disturbances (most often peptic ulcer), it was noticed that several patients did not respond to the regimen as well as might have been expected. Investigation revealed the fact that although these patients generally adhered to the diet, the discomfort produced by the side reactions of the drugs induced them to stop medication entirely or to take it haphazardly."

MATERIAL AND METHOD

"Twenty patients (14 private and 6 clinic patients) were chosen who, in the absence of complications, had shown unsatisfactory response to a prescribed regimen of diet, anticholinergic, sedative (phenobarbital) and antacid. In addition to gastrointestinal symptoms, these patients all had in common varying degrees of emotional disturbances and they all had voluntarily stopped or interrupted their medication because of undesirable side-effects. These reactions were in descending order of incidence: dry mouth, blurred vision, drowsiness or beclouding of the mind, and interference with bowel and bladder function."

"In each case, the patient was started on tridihexethyl iodide with meprobamate in place of the previously administered anticholinergic-sedative combination, the diet and antacid remaining unaltered. The method of administration was the same as for the previous drugs; i.e., one tablet with each meal and one or two tablets at bedtime."

RESULTS

"... the results of treatment (Table II) with tridihexethyl iodide and meprobamate were excellent or good in 18, or 90 per cent of the cases and poor or questionable in 2, or 10 per cent. It will be noted ... that both of these patients were 'functional' cases."

No. of Patients	Response			Side Reactions			
	Excellent	Good	Poor or Questionable	Drowsiness	Dry Mouth	Other	Total
20	15 (75%)	3 (15%)	2 (10%)	2 (10%)	1 (5%)	0	3 (15%)

SIDE REACTIONS: 2 patients noted mild drowsiness and dry mouth, one patient dry mouth only. In no case were the symptoms severe enough to warrant diminishing the dose.

COMMENTS

"The encouraging clinical results of this investigation point up the fact that although poor progress is frequently due to poor patient cooperation, we can do much to improve this situation by recognizing the validity of the patients' complaints with respect to side reactions and then prescribing medication with a low incidence of unpleasant effects."

"Since this group of patients was chosen because of sensitivity to anticholinergic-sedative, statistical evaluation of side reactions to the medication used in this study is not feasible. The reduction from 100 per cent of side reactions attributable to the previously used medication to only 15 per cent with tridihexethyl iodide-meprobamate, however, is indeed noteworthy."

ILLUSTRATIVE CASE

X-ray examination revealed a hiatus hernia (about one inch in diameter) and a large gastric ulcer (Fig. 1).

FIG. 1—*X-ray (Case #17) at time of presentation (11 December 1957). P-A view showing large ulcer crater (arrow) on lesser curvature of stomach. Note also, small residue of barium in hiatus hernia.*

FIG. 2—*Same patient (18 March 1958). After 10 weeks' therapy (see text). Note complete disappearance of ulcer crater.*

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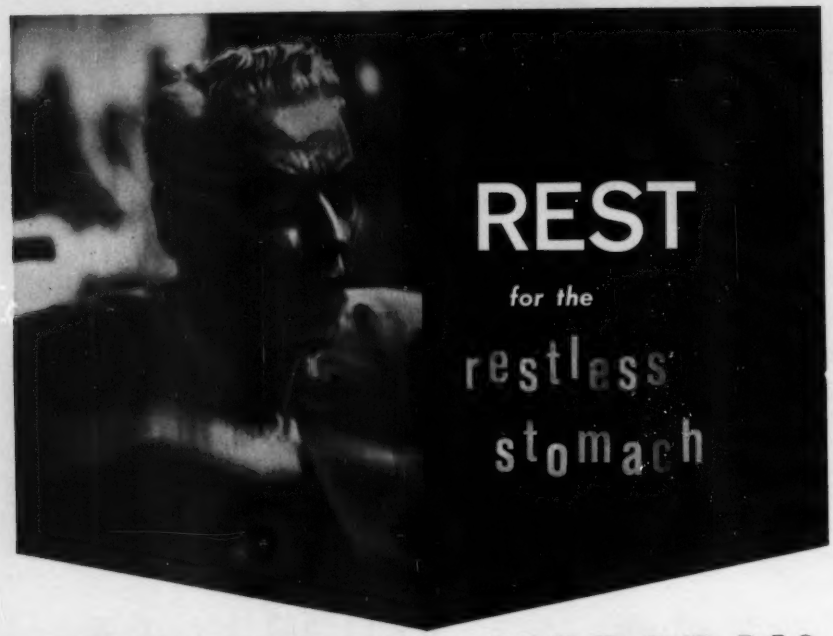

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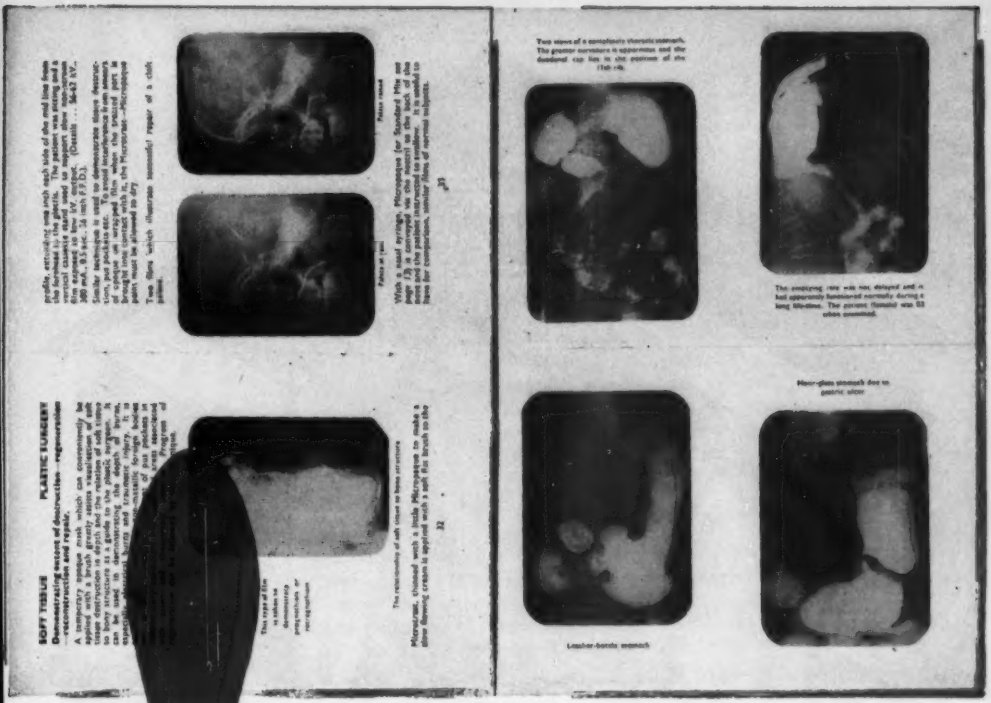

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SUMMARY OF CASES

Clinical Diagnosis – Peptic Ulcer – Gastritis – Gastroenteritis – Colitis – Functional Bowel Syndrome – Duodenitis Hiatus Hernia (Symptomatic) – Irritable Bowel Syndrome Pylorospasm – Cardiospasm – Biliary Tract Dysfunctions

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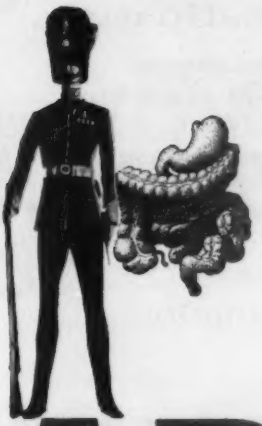

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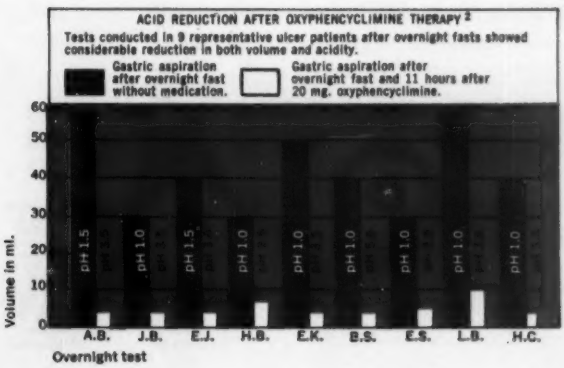

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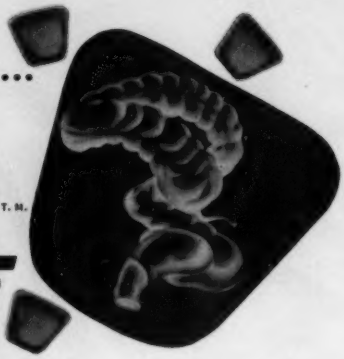

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VOLUME 32 OCTOBER, 1959 NUMBER 4

GASTROINTESTINAL SYNDROMES OF VASCULAR ORIGIN*

DENNIS ROSENBERG, M.D.†
New Orleans, La.

For years, gastroenterologists have been aware of a number of abdominal conditions that have, as their underlying basis, a pathologic process in the vascular system. Until recently, treatment of these maladies has been largely unsatisfactory because of difficulties of early diagnosis and inadequacy of surgical efforts. Now, with the amazing advances in vascular surgery during the past five years, re-evaluation of these syndromes, often seen first by the gastroenterologist, seems warranted.

Abdominal aneurysms:—Abdominal aneurysms are almost exclusively arteriosclerotic in origin, developing invariably distal to the origin of the renal arteries. Notorious for their silence, these aneurysms are often an incidental discovery during examination for an unrelated complaint. Only about one-third of the patients have symptoms. The mere presence of symptoms is of serious prognostic significance, as survival after their onset is usually limited to about three years without operation. Twenty-five per cent of the patients die from rupture within one year.

The commonest symptom is a throbbing pain, often boring through to the back. Severe pain in the back invariably indicates leakage. Occasionally, the first symptom may be referred to the gastrointestinal tract such as vague dyspepsia, constipation, symptoms of partial obstruction, anorexia, and loss of weight.

The ever-present, expansile, pulsating mass, especially notable in the upper left portion of the abdomen with the patient prone may be easily detected. Rupture and preliminary leakage are associated with a more severe, constant, gnawing pain. Whereas the site of leakage is generally the retroperitoneal

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, New Orleans, La., 23, 24, 25 October 1958.

†From the Department of Surgery, Tulane University, School of Medicine, New Orleans, La.

space, occasionally it is the duodenum or jejunum, in which locations, the diagnosis becomes considerably more difficult. Shock, abdominal distention, and the usual manifestations of severe intraintestinal hemorrhage are present. Pain, although usually excruciating, may be minimal, and the abdomen, at first tender or rigid, becomes softer as ileus progresses. Early diagnosis is facilitated by the presence of ecchymosis of the lower abdominal wall from leakage of blood from the retroperitoneal space along the psoas muscle. Widening of the psoas shadow is often seen. Peritoneal irritation and abdominal distention are later signs indicative of a passage of blood into the peritoneal cavity.

Resection of the aneurysm before rupture, with restoration of continuity by grafting, is the only logical form of treatment. It is associated with a case fatality rate of 2 to 10 per cent. Once leakage or frank rupture has occurred, prompt emergency operation may result in a salvage rate of approximately 50 per cent. Contrary to general belief, leakage may be slow, often lasting for days, so that there is time for surgical intervention.

Dissecting aneurysms:—Dissecting aneurysms are actually dissecting hematomas and usually begin with a tear in the intima, with subsequent splitting of the media of the aorta. The commonest site is in the first portion of the ascending aorta, but the process may originate in the descending aorta, distal to the subclavian artery, the blood tunnelling its way down through the media, with dissection often as far down as the femoral arteries. In these instances, the abdominal branches of the aorta may become occluded or sheared off, and in those cases in which dissection progresses more slowly, days or even weeks may go by before final perforation and death occur. Occasionally, the dissection "heals" itself by spontaneous re-entry into the true aortic lumen.

If the lower thoracic or abdominal aorta is involved, symptoms of an abdominal catastrophe may appear. Extremely severe pain in the chest and upper abdomen, often unrelieved by opiates, is characteristic. The clinical manifestations are confusing, and the diagnosis is unsuspected until interference with the major branches of the aorta and peripheral blood flow to the extremities becomes obvious. The presence of nausea, vomiting, abdominal pain, rigidity, diarrhea, and bloody stool indicates dissection into the mesenteric arteries.

Pain, beginning in the substernal and epigastric areas, extending into one or both sides of the abdomen, and accompanied by cold, pulseless lower extremities, should arouse suspicion of a dissecting aneurysm. Hematuria is often present, and hypertension is usual.

Ninety per cent of dissecting hematomas are acute but the other 10 per cent are subacute or chronic and allow time for diagnosis by aortography. The dye is heavily concentrated in the true aortic lumen, the false passage appearing as a surrounding superimposed channel. Surgical procedures are designed

to create a re-entry passage into the aortic lumen by excision of a small segment of the intima and media above and obliteration of the false passage below by circumferential suture.

Mesenteric arterial disease:—The visceral manifestations of occlusion of the intestinal blood vessels are well known. The case fatality rate, as high as 80 per cent in most series, is attributable mainly to the difficulties involved in early diagnosis and institution of adequate surgical treatment. Mesenteric arterial occlusion may be due to an embolus, thrombosis, or an aneurysm, and the clinical picture may be acute or chronic, depending on the size of the vessel involved, the rate of closure, and the adequacy of collateral circulation. Embolism originates from a fibrillating heart or a mural thrombus, whereas thrombosis of the vessel may be associated with an arteriosclerotic plaque in the vessel itself or at its origin. Aneurysm and trauma play a lesser role.

Sudden occlusion presents a dramatic and shocking picture. Severe pain and vomiting are usual, and leucocytosis is pronounced. Bloody diarrhea is followed by shock and gradual distention, which may take as long as five to eight days to develop fully. Characteristically, the physical findings in the early stages are minimal. Loss of bowel function and obstruction are followed by perforation and peritonitis, with death often inevitable.

In chronic thrombosis of the superior mesenteric artery, symptoms may be present for weeks before signs of infarction appear. This syndrome of chronic mid gut ischemia, also known as intermittent mesenteric claudication, is characterized by abdominal pain, which is colicky initially but later becomes typically constant and is precipitated by meals. Altered bowel habits, occult blood in the stools, and loss of weight are usual findings. Diarrhea occurs, probably as a result of malabsorption of fat.

In contrast, acute ischemia is followed by vomiting, bloody diarrhea, and peripheral collapse. Chronic mid gut ischemia is likely to occur in patients in whom the main stem of the artery is occluded by arteriosclerotic thrombosis.

Surgical treatment, up to the present, has been directed toward resection of the infarcted intestine. It is important to realize that the superior mesenteric artery is approximately 1 cm. in diameter at its origin, and gradually narrows to approximately 8 mm. over a distance of 10 cm. It is, thus, about the size of the femoral artery. It is amenable to direct surgical approach by displacement of the transverse colon upward and exertion of traction on the jejunum and mesentery. The artery may be mobilized and opened after incision of the overlying peritoneum. Embolectomy and thromboendarterectomy are likely to improve the dreadful prognosis of mesenteric occlusion if diagnosis can be suspected early, before extensive infarction has occurred.

Visceral arterial aneurysms:—Although these are not common, they have been described in the splenic, superior mesenteric and hepatic arteries.

Splenic aneurysms:—In recent years, more importance has been given this condition, and a more encouraging prognosis has been noted as a result of early recognition of its clinical pattern and prompt operation. The lesion, which is present in the main trunk of the splenic artery, varies in size from that of a pea to a coconut. Contrary to the usual predominance in men of approximately 5 to 1 for arterial aneurysms in other sites, aneurysms of the splenic artery are found twice as often in women as in men. In a recent review of 190 cases, 127 or 60 per cent were in women. Also of unusual interest is the fact that 85 per cent were in women younger than 45 years. A further peculiar feature of this condition is the frequent occurrence in pregnant women. Fifty-six per cent of women with aneurysms in this series were pregnant at the time the diagnosis was made. Splenomegaly occurs in about 50 per cent of patients.

Before rupture of the aneurysm, symptoms are few and nonspecific. Epigastric discomfort, often mistaken for peptic ulcer, may be present. Forward bending appears to aggravate the pain, which may continue intermittently for years. In approximately 20 per cent of patients, a palpable mass may be felt. With rupture, acute and delayed clinical courses can be recognized. The aneurysm initially ruptures into the lesser sac; this produces severe pain that extends to the back and left shoulder, with shock and signs of peritoneal irritation. As the lesser sac and retroperitoneal space are limited, bleeding is tamponaded, and clotting occurs. This state is seldom fatal, and improvement is usual. Hours or days, even weeks later, secondary rupture occurs into the free peritoneal cavity, stomach, or colon, and profound collapse ensues with the clinical picture of frank internal hemorrhage. Familiarity with the clinical manifestations and suspicion of the condition in patients with concealed hemorrhage during the later stages of pregnancy will lead to a higher incidence of preoperative diagnosis. On fluoroscopic examination, a pulsating tumor, perhaps partially calcified, may be seen, or a filling defect may be observed in the posterior portion of the stomach. Aortography has been used to demonstrate the aneurysm unless it has already been occluded by a thrombus. If the diagnosis of splenic arterial aneurysm is made or suspected, the treatment of choice is resection of the artery and splenectomy. After rupture, prompt operation, of course, is essential. If rupture occurs during pregnancy, there is no reason to empty the uterus during the laparotomy. In patients who are extremely poor risks, it may be necessary to limit the operation to simple ligation of the splenic artery.

The final group for discussion consists of patients with massive intraintestinal hemorrhage due to direct erosion into the intestine. Abdominal aortic aneurysms have, on rare occasions, ruptured directly into the overlying duodenum or jejunum, which has become adherent to the sac.

Cases of right iliac aneurysm, rupturing into the third portion of the duodenum, have also been reported. A mycotic element is responsible for a good proportion of these ruptures, as perforation into the digestive tract is otherwise rare.

With the large number of aorta-iliac resections now being performed for aneurysm or arteriosclerotic occlusive disease, reports of fatal gastrointestinal hemorrhage, months after reparative operation, are filtering into the literature. In these instances, the duodenum, jejunum, and even the sigmoid have become attached to the suture line or the plastic prosthesis, with slow perforation of the intestine at this point. It is important to reconstitute the posterior part of the peritoneum over the prosthesis in order to avoid this complication.

Finally, an extremely rare cause of massive alimentary tract bleeding has been noted. A 32-year old man had had a Hufnagel valve inserted into the aorta ten years previously for severe aortic insufficiency. He was admitted to the hospital in shock with severe uncontrollable hemorrhage. At autopsy, a false aneurysm had formed just proximal to the valve and had ruptured into the esophagus.

Summary

A number of pathologic processes of vascular origin have symptoms manifesting gastrointestinal disease. The diagnosis of these conditions is often difficult to establish in the early stages, but with the advances in vascular surgery during the past few years, it has become increasingly more important to bear these syndromes in mind.

A brief review of abdominal aortic aneurysm, dissecting aneurysm, splenic arterial aneurysms, mesenteric thrombosis and rarer causes of massive gastrointestinal bleeding has been presented.

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Discussion

Dr. I. Snapper:—I never object to operations of arteriosclerotic aneurysms although I am not convinced that we actually know the survival time of such patients. The greatest danger which threatens these patients is repeated palpation.

Patients with abdominal aneurysms who have been examined by the participants in postgraduate courses in cardiovascular diseases, have a very high fatality. In my opinion only the patients with undiagnosed abdominal aneurysms who are never palpated, have a normal survival time. This survival time by definition is not known.

The results of the operation, however, as published are so favorable that one cannot resist the wishes of the vascular surgeons.

Dr. O. H. Wangensteen:—I do not believe this segment of surgery is in quite the experimental stage that Dr. Snapper indicated it is; in fact, as all of us, who have any familiarity with this kind of surgery, know it is interesting to reflect how the hand of the surgeon was restrained by the shadow of the pathologist for so many years. In fact, it is odd that attempts had not been made long years ago to resect the lateral, globular aneurysm of the aorta. Surgeons, following the teachings of pathologists, believed that if such resections were made, the "weakened" aortic wall would balloon out, presently in another place.

While at the Johns Hopkins Hospital, the late Mont Reid, one of the great vascular surgeons of his day, wrote about 20 papers on the management of aneurysms without proposing some of the procedures current today. Efforts were directed largely at ligating large blood vessels proximal or distal to the dilatation. As Dr. Rosenberg said, today such aneurysms are removed and replaced largely with prosthetic tubes. This has been a tremendously interesting development in surgery.

In the hands of Drs. DeBakey and Cooley, and a number of other American surgeons, rapid strides are being made in this area of surgery. A fairly large number of patients have been operated upon by homograft and prosthetic graft technics, now more than five years ago; a large number of these continue to do well.

Any surgeon could spend a few days very profitably in one of the clinics where this kind of surgery is being done, to see what these enterprising surgeons are doing.

Dr. Rosenberg talked also of the superior mesenteric artery syndrome. At the Massachusetts General Hospital, a few successful endarterectomies of the superior mesenteric artery have been done for this condition. Klass (1951) of Winnipeg had reported an unsuccessful attempt several years before. The

main thing as Dr. Rosenberg emphasized is to recognize the presence of obstruction of the superior mesenteric artery early enough to do something about it. Shaw and his associates at the Massachusetts General Hospital, in recent years, have done several successful embolectomies on the superior mesenteric artery for arterial occlusion.

A development in our own clinic has come about in this connection which may come to have some pertinence for this discussion. One of our young surgeons, Eugene Bernstein, has shown that one can get aortograms by an intravenous injection [*Surgery* 44:529, (Sept.), 1958]. Whereas he gets good pictures of the thoracic and abdominal aorta by these injections, he has not yet been able to visualize the superior mesenteric artery with any suggestion of regularity. He will undoubtedly perfect some aspects of the technic to the end that, intravenous injection will come to supplant direct puncture of the aorta in many situations in which an aortogram is desired. We have another young surgeon, Richard C. Lillehei, who is working in the difficult field of excising and replacing the intestine. He divides the superior mesenteric vein and artery, and puts the intestine in a sterile container in the refrigerator. After a lapse of a few hours, he can place the bowel back in its former position and, with survival in a large number of dogs, thus operated on.

Dr. Rosenberg's was a very nice and timely presentation. I hope he will find time to say something about the expected longevity of patients, having aneurysms of the aorta removed as contrasted with the expectancy of patients having these lesions, who do not undergo surgery.

Dr. Robert M. Moore (Galveston, Tex.):—Apropos of Dr. Rosenberg's discussion, two days ago I joined one of our younger men in an operation, chiefly to give an opinion as to whether I thought the superior mesenteric artery could be sacrificed safely. The patient was a man of 66 years with a strange complaint of postprandial pain for ten years. It had become worse of late, occurring after every meal, until he had largely quit eating and had lost 40 pounds. All diagnostic studies were negative, save that there was a murmur over the area of origin of the superior mesenteric artery, and the aortogram showed a narrowing of its orifice from the aorta. The case was presumed to be one of "abdominal angina".

At operation it was found that there were neither visible nor palpable pulsations in the celiac or superior mesenteric arteries, or in their branches. There was an enlarged inferior mesenteric artery with a strong pulsation. Simultaneous pressure readings showed a systolic pressure of 170 mm. mercury in the abdominal aorta but only 30 mm. in a second division of the superior mesenteric trunk. The splenic artery had no visible or palpable pulsation and the measured pressure was only 20 mm. mercury. When the splenic artery was cut across there was only a slow welling of blood from the cut end. A by-pass bifurcation homograft was inserted from aorta to superior mesenteric and celiac arteries.

The matter of superior mesenteric artery insufficiency is another vascular syndrome which may grow in importance. In this case the gastrointestinal tract apparently was receiving virtually its entire arterial supply from the inferior mesenteric artery. Detailed examination of arterial pulsations may become important in many surgical explorations.

Dr. Dennis Rosenberg:—It is always nice to begin a conversion by starting with the surgeon, and I am pleased to hear Dr. Moore has become converted to this type of surgery. I hope the internists are next.

Dr. Snapper, in regard to your question of survival rate and mortality rate if these patients are not operated upon: this evolves into rather a philosophical question.

Estes reviewed 97 aneurysms which had not been operated upon, and were followed for a number of years. Approximately 50 per cent of them were dead within three years, and, in Crane's series if the aneurysms were large, over 7 cm., 80 per cent were dead in one year.

Now, apparently there are other features besides the presence of the aneurysms which must be considered. The state of the vascular system as a whole is all important; the more arteriosclerosis, the higher the over all death rate.

Dr. Boyd in England emphasizes the size of the aneurysm feeling that anything less than 6 cm. in diameter can be watched and those more than 6 cm. in diameter (a crude type of measurement through the abdominal wall) is a dangerous tumor and should be resected at that stage.

Obviously, it is better to resect while the aneurysms are intact, for after rupture the mortality rate increases 50 to 70 per cent.

So the question of how long an aneurysm may be ignored without surgery is I believe unanswerable. All aneurysms that give symptoms certainly need prompt resection. Small dilatation may perhaps be watched—the larger ones should be operated upon.

VITAMIN B_{12} AND THE MALABSORPTION SYNDROME*†

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In the course of investigation of more than 100 patients with macrocytic anemia, malabsorption of Vitamin B_{12} which was not corrected by administration of intrinsic factor was observed in 21 instances. Malabsorption was detected by means of the Schilling test in which Vitamin B_{12} labeled with Co^{60} is administered. The clinical diagnosis in these patients prior to measurement of the absorption of Vitamin B_{12} had been pernicious anemia, nutritional macrocytic anemia or sprue. Further study of these subjects indicated a wide variety of absorptive defects. None of the subjects had a family history of celiac disease and only one a history suggestive of idiopathic steatorrhea. These patients were all in the older age group. In every instance, satisfactory hematologic response followed oral administration of Vitamin B_{12} in large amounts and there was concomitant improvement in general clinical condition. In some of the patients folic acid was equally effective as a therapeutic agent.

Materials and Methods

The patients were adults seen in the Nutrition Clinic of Tulane University and in Charity Hospital in New Orleans. Each was personally attended by at least one of the authors. All of the diagnostic studies were carried out on a metabolism ward to ensure accurate collection of specimens. Concentration of Vitamin B_{12} in serum was estimated by the microbiologic method of Rosenthal and Sarett[1]. Absorption of Vitamin B_{12} was determined with the Schilling test

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as originally described[3]. This procedure is carried out as follows: 2μg Co^{60} B_{12} (0.5 microcuries radioactivity) is given orally followed in two hours by the parenteral administration of 1,000 μg of the nonradioactive vitamin. Urine is collected for 24 hours and radioactivity measured. After a period of 72 hours or more, the same dose of labeled Vitamin B_{12} is administered, together with a source of intrinsic factor. This is followed by the parenteral flushing dose of Vitamin B_{12} and collection of urine for 24 hours for determination of radioactivity as described above.

Levels of carotene and Vitamin A in serum were determined by a modification of the method of Paterson and Wiggins[3]. The Vitamin A tolerance test consisted of administration of 5,000 international units per kilogram of body weight of an oily solution of Vitamin A. Breakfast of standard amounts of orange juice, cereal, white bread, jelly, sugar, skim milk and coffee was given immediately after the dose of Vitamin A. Blood samples were obtained during fasting and at 3, 6 and 9 hours after administration of the vitamin. In many instances a sample of blood was obtained after 24 hours. Lunch was given immediately after the 3-hour blood sample. The standard menu included broiled ground beef pattie, white boiled potato or rice, canned beets, white bread, jelly, sugar, skim milk and coffee.

Glucose tolerance tests were carried out as follows: 100 gm. of glucose was administered orally in the post absorptive state and glucose concentration in blood was determined before and at ½, 1, 2 and 3 hours thereafter.

In the water diuresis test, no fluid was given after 6:00 p.m. and the volume of urine passed between 10:00 p.m. and 7:00 a.m. was measured. At 7:00 a.m. 20 ml. of water/kg. of body weight was given orally and urine was collected hourly until noon; no food being permitted during this period. The volume of the hourly specimens was compared with the volume of the night urine. In normal subjects, the volume of one of the hourly specimens after the water load exceeds the night volume.

Fecal fats were determined by the method of van de Kamer et al[4]. The standard diet for fat balance studies furnished 100 gm. of fat daily except in one instance in which only 50 gm. of fat was provided. Feces were collected for four days, carmine markers being used to assist in accuracy of collection. Results are expressed as the per cent of dietary fat absorbed, or the coefficient of absorption (C.A.) $= \frac{\text{fat ingested} - \text{fat excreted}}{\text{fat ingested}} \times 100$. The coefficient of absorption is greater than 95 per cent in normal subjects.

Results

The patients ranged in age from 53 to 85 with an average of 65 years. There were 8 white males, 7 white females, 3 negro males and 3 negro females.

Anorexia was a prominent complaint in practically all of the patients and 17 had lost weight. Many of the patients had been eating diets of poor quality for months or years prior to development of their illness. Seventeen of the patients had glossitis and 11 gave a history of diarrhea. Several of the patients complained of paresthesias but no objective evidence of neurologic disease was found in any subject.

Laboratory findings in these patients are given in Table I. A macrocytic anemia was present in all subjects and the bone marrow was megaloblastic in all but three (D.S., A.B. and L.D.); in one of these the anemia was mild. Achlorhydria after histamine stimulation was observed in 8 subjects.

Serum concentration of Vitamin B_{12} was low, between 20 and 60 $\mu\mu$g/ml. in each of the 11 patients in whom it was measured during hematologic relapse. These levels are in the range found in pernicious anemia. Normal concentrations in our laboratory are above 80 $\mu\mu$g/ml. and may be as high as 700 $\mu\mu$g/ml.

Roentgenologic study of the small intestine after administration of barium was carried out in 13 patients. Evidence of a "deficiency" pattern was noted in only five. Changes consisted of dilatation and smoothing of the intestinal contour with segmentation and clumping of barium.

The Schilling test indicated malabsorption of Vitamin B_{12} in each of the subjects; in 17 subjects less than 3 per cent of the administered dose of $Co^{60}B_{12}$ was excreted, in four, excretion ranged from 3.2 to 5.9 per cent. Intrinsic factor did not increase excretion significantly in any instance. In our experience, normal persons excrete more than 6 per cent of a 2 μg dose of $Co^{60}B_{12}$ given orally. Patients with pernicious anemia excrete less than 2 per cent and usually less than 1 per cent of the dose when Vitamin B_{12} is given alone but normal amounts when intrinsic factor is administered with the vitamin. Excretion may be decreased by infection or renal disease but these conditions were not present in the subjects of this study.

A glucose tolerance test was carried out in 17 patients. The results are expressed as the difference between the fasting and peak values (Table I). The curves were "flat" in 9 instances if one accepts a rise of less than 40 mg. as abnormal. Gardner[5] has reported that about 40 per cent of normal subjects will demonstrate a flat curve if this criterion is used. He has stated also that if an increase in excess of 25 mg./100 ml. is considered to be the normal rise, 20 per cent of normal subjects will exhibit a flat curve. Six of our patients had a flat curve using this latter criterion.

Gaddie and associates[6] have stated that the chief value of the glucose tolerance test in the diagnosis of intestinal malabsorption is in the detection of a diabetic type of curve. This response in a patient with no family history of

TABLE

Patient	Year	Age	Sex	Race	Hgb. gm./100 ml.	RBC ml./cu. mm.	MCV cu. micra	Bone Marrow Megaloblastic	Histamine Achlorhydria	Serum Concentration Vitamin B_{12} μ μg/ml.
J.G.	43	60	M	W	13.3	3.46	106	+	−	
	46				9.4	2.77	111	−	−	
	57				15.0	4.60	100			
A.S.	50	70	M	W	6.3	1.17	153	+	−	
	51				7.7	1.65	130	+	−	40
	57				14.8	4.40	105			
M.B.	52	66	F	W	3.8	0.73	146	+	−	
	54				8.2	2.31	112	+		20
	56				13.4	4.65	90			
D.S.	57	81	F	W	5.8		108	−	−	
D.D.	49	67	M	W	4.1	0.94	148	+	−	
	57				13.7	4.40	95			
R.R.	51	53	F	N	10.0	3.10	106	−	+	
	52				9.3	2.86		+		30
	57				11.8	3.80	100			
L.T.	53	60	M	N	6.0	1.92	100	+	+	
	57				14.4	4.60	98			
W.D.	56	73	M	N	6.1	1.26	142	+	−	
A.B.	54	58	F	W	11.0	2.42	132	−	−	60
	56				14.0	4.36	99			
E.S.	54	79	F	N	10.0	3.21	110	−	+	
	54				3.6	1.13	115	+	+	30
	57				14.0	4.70	95			
O.L.	57	79	M	W	6.5	1.39	152	+	+	40
C.L.	57	58	M	W	4.3	1.06	122	+	+	
J.M.	54	63	M	W	5.8	1.50	107	+	−	50
	56				15.6	4.62	100			
H.G.	42	54	M	W	10.8	2.95	108	+	−	
	46				9.5	1.94	144	+	−	
	57				13.0	3.98	95			60
J.D.	57	58	M	W	5.0	1.64	97	+	−	
R.C.	56	57	F	W	8.9	1.90	142	+	+	50
E.B.	50	54	F	W	3.8	1.17	153	+		
	56				12.1	4.78	80			30
L.D.	54	85	F	W	7.2	1.68	128	−	+	
	56				10.4	3.11	100			
A.T.	47	53	F	N	4.0	1.37	94	+	+	
	54									40
	57				11.5	3.70	100			
V.A.	56	65	M	N	7.2	1.99	115	+	−	
E.D.	52	58	F	W	5.5	1.58	120	+	−	
	53				4.7	0.99	121	+	−	
	58				12.1	3.79	79		−	

C.A. = coefficient of fat absorption (See text).

Glucose Tolerance test Maximum glucose Increase mg./100 ml.	Carotene Concentration (Fasting) μg/100 ml.	Vitamin A Tolerance Test					Steatorrhea	Schilling Test	
			Hours					% Urine radio-activity in 24 hrs.	
		Fasting	3	6	9	24		Vitamin B_{12} Alone	Vitamin B_{12} and intrinsic factor
33							Microscopic	0.8	0.3
9							Microscopic		
10	20	63	82	272	196			0.4	0.1
99	31	33	62	103	60	49	C.A. = 90	0.7	0.4
	53	12	324	240	86			3.3	3.7
40	128	75	83	392	364			5.9	4.6
								1.6	2.0
90	226	84	256	570	1130		C.A. = 96	2.1	3.3
43	68	36	45	77	90	43	Microscopic	1.5	0.1
15	140	46	214	1005	426		Microscopic	1.9	1.1
								2.4	2.6
93	52	33	453	167	190		C.A. = 88	4.7	4.0
50	88	54	48	54	208		C.A. = 92	1.4	1.3
30	47	15	11	97	46	17		0.1	0.2
0							Gross	0.6	0.1
7	110	28	244	362	147		C.A. = 86	0.5	1.0
27	30	22	220	200	76	28	C.A. = 88	0.2	0.5
21							Microscopic		
102	98	39	99	384	136	70		1.3	0.7
54	67	75	114	129	104	92	Microscopic	0.2	0.1
	52	50						0.1	0.0
111	40	30	46	71	94	42	Gross C.A. = 60	2.2	1.6
24									
15	20	23	48	26	33		C.A. = 88 (I^{131} triolein)	3.2	2.7

diabetes would suggest that the etiology of the malabsorption was pancreatic exocrine insufficiency rather than primary intestinal dysfunction. In two of our patients (M.B. and O.L.) a diabetic type of curve was obtained. The diabetes was mild in both instances and was controlled readily by slight restriction of carbohydrate intake. Two patients (E.B. and V.A.) exhibited abnormally high levels of blood glucose at 1 hour after administration of the test meal. Both of these subjects had normal blood glucose concentrations in the fasting state, and in both instances the glucose concentration had returned to normal levels within two hours after administration of the test dose. In patient E.B. the glucose tolerance test had been flat prior to therapy.

Malabsorption of Vitamin A was observed more often than that of glucose. With the tolerance test used in this study, normal subjects usually show a rise in concentration to at least 300 μg/100 ml. Of the 16 subjects in whom the Vitamin A tolerance test was carried out, the maximum concentration of Vitamin A in serum was less than 300 μg/100 ml. in 9 instances.

It has been reported that the increase in serum Vitamin A is dependent to some extent upon the fasting Vitamin A level[7]. There does not appear to be any relation between the concentration during fasting and the peak value in the present study. Vitamin A concentration at the end of 24 hours resembled that obtained prior to the test.

Normal values for Vitamin A in serum during fasting range from 25 to 75 μg/100 ml. in our laboratory, normal values for carotene from 50 to 200 μg/100 ml. Only 4 of 17 patients had low levels of Vitamin A and only 6 of 17 had low carotene levels. The fasting carotene level was not of much value as a screening procedure for detection of the malabsorption syndrome as has been reported by others[8].

The level of calcium in the serum was measured in approximately half of the patients and was found to be low in only one instance (W.D.). Tetany was not observed in any subject nor was there evidence of osteomalacia on x-ray examination. Osteoporosis, when present, was presumably senile in type and explicable on the basis of other mechanisms.

The water diuresis test was carried out in 8 patients. The response was normal in only one instance. In others, the volume of none of the hourly specimens exceeded the night volume. This test appears to have merit as a screening procedure for the malabsorption syndrome but has no specificity as it is positive in a number of other pathologic states.

Gross steatorrhea was present in only two subjects. In one of these, a fat balance study indicated that only 60 per cent of dietary fat was absorbed. Microscopic examination of the stool showed the presence of considerable fat in 6 patients. In six other subjects fat balance studies were carried out and in five of these the coefficient of fat absorption was less than 95 per cent. In one

additional subject (E.D.) triolein labeled with I^{131} was administered; only 88 per cent of the test dose was absorbed. One patient (L.T.) had normal absorption of fat. This patient would certainly have been diagnosed as having pernicious anemia prior to the development of methods for studying Vitamin B_{12} absorption.

Diagnosis

The original diagnosis in 8 of the 21 subjects in this study was sprue. In each of these patients microscopic or gross evidence of steatorrhea was noted. Malabsorption of Vitamin B_{12} is common in the sprue syndrome but normal absorption is encountered not infrequently.

Six patients were thought to be suffering from nutritional macrocytic anemia before the Schilling test was performed. Each of these patients had consumed a marginal diet for long periods of time prior to the onset of his illness. The occurrence of an event such as a respiratory infection or emotional upset seemed to account for anorexia which led to a more inadequate intake of food. In view of these findings, the diagnosis of nutritional macrocytic anemia seemed warranted in the absence of steatorrhea and the presence of free acid in the gastric juice.

Seven patients were considered to be typical examples of pernicious anemia. In these subjects, the diet appeared to be adequate. Histamine achlorhydria was observed and there was no obvious steatorrhea.

The following case is illustrative of the patients who were thought to have nutritional macrocytic anemia prior to performance of the Schilling test. Early observations in this patient were reported previously[9] at which time the nutritional origin of this condition was questioned.

Case 1:—A 66-year old white woman (M.B.) was admitted in April, 1952. Two and one-half months prior to admission, she experienced fever, headaches, nausea and occasional vomiting lasting for several days. Her appetite had always been poor and decreased markedly following the febrile episode. She grew progressively weaker and lost 15 lbs. On admission, the patient appeared chronically ill and had evidence of moderate weight loss. The skin and sclera had a yellowish tinge and the mucous membranes were very pale. The tongue was markedly red and smooth and slight cheilosis was present. The erythrocyte count was 0.73 million/cu. mm.; hemoglobin, 3.8 gm./100 ml.; mean corpuscular volume (MCV), 146 cubic microns, and mean corpuscular hemoglobin concentration (MCHC), 34 per cent. Serum bilirubin was 1.8 mg./100 ml. The bone marrow was megaloblastic. Free acid was found on gastric analysis on two occasions.

Two blood transfusions were given, with only temporary effect upon the blood picture. Large oral doses of Vitamin B_{12} were then administered. An

excellent symptomatic and hematologic response was obtained and she was discharged with the diagnosis of nutritional macrocytic anemia. No additional oral B_{12} was prescribed.

Shortly after discharge, she complained of a sore tongue, which was found to be atrophic even though her diet now appeared to be adequate. The blood count slowly declined and stabilized at a subnormal level: erythrocytes, 3.7 million; Hgb., 13.9 gm. and hematocrit, 40 per cent. In view of the apparent relapse, oral administration of Vitamin B_{12} was resumed in November, 1952 and continued through March, 1953. During this period the patient was asymptomatic and hematologic values were normal except for slight macrocytosis. At this time, therapy with Vitamin B_{12} was discontinued. The blood count gradually decreased and in April, 1954, hemoglobin was 8.2 gm./100 ml., MCV, 112 cu. μ; MCHC, 31 per cent. The bone marrow was again megaloblastic. Administration of large oral doses of B_{12} resulted in a good response which has been maintained with 1 mg. of the vitamin orally once a week. The level of Vitamin B_{12} in the serum decreased to about 20 μ μg/ml. on several occasions when therapy was withheld.

In April, 1956 the glucose tolerance test showed a diabetic curve (Table I). Concentration of carotene in the serum was 31 μg/100 ml. The Vitamin A tolerance curve was flat, and the water diuresis test was positive. X-rays of the small intestine following a barium meal were normal.

In September, 1957 a Schilling test was performed. Excretion was 0.7 per cent after Vitamin B_{12} alone and 0.4 per cent after Vitamin B_{12} in combination with intrinsic factor. After tetracycline had been administered for four days, excretion of Vitamin B_{12} was 1.1 per cent. The gastric juice of this patient was given to a patient with pernicious anemia as part of the Schilling test and increased the excretion from 0.9 per cent with Vitamin B_{12} alone to 12.8 per cent. These findings demonstrate that intrinsic factor was present in the gastric juice.

When this subject was first seen, the poor dietary history seemed to justify a diagnosis of nutritional anemia. The relapse which occurred while she was receiving a good diet, however, suggested that malabsorption was important in the etiology of her illness. At the time of relapse, the low serum concentration of Vitamin B_{12} indicated deficiency of this vitamin. Response to therapy was excellent both clinically and hematologically. Subsequently, the patient became obese and the glucose tolerance curve was found to be diabetic in type. The diabetes was mild and easily controlled by dietary means.

The next case is representative of the patients who were thought to have pernicious anemia prior to administration of the Schilling test.

Case 2:—A 53-year old colored woman (R.R.) was seen in December, 1951. For a few months prior to admission she had complained of epigastric dis-

comfort, weakness and paresthesias of the hands and feet. On physical examination she appeared to be adequately nourished and no gross abnormalities of any of the bodily systems were detected. The mucous membranes were somewhat pale. Hemoglobin was 10.0 gm./100 ml.; erythrocyte count, 3.1 million/cu. mm.; MCV, 106 cu. μ and MCHC, 30 per cent. There was no free acid in the gastric juice after histamine stimulation. Bone marrow examination in January, 1952 was not diagnostic. On further questioning, the patient stated that two days prior to aspiration of the bone marrow she had begun eating large amounts of liver on the advice of a fellow passenger on a bus. The patient was followed without therapy. In June, 1952 the level of Vitamin B_{12} in the serum was 40 μ μg/ml. in November, 1952, 30 μ μg/ml. At this time glossitis was present and the hemoglobin had decreased to 9.3 gm./100 ml. Bone marrow examination showed typical megaloblastic arrest. A good response followed therapy with Vitamin B_{12} and she has remained in remission while taking the vitamin. In February, 1957 a Schilling test revealed a malabsorption pattern (Table I).

The diagnosis of sprue was made in patients who had megaloblastic anemia and diarrhea with an increase in fat in the stools. In most instances, free hydrochloric acid was found in the gastric juice following histamine stimulation. The following patient is a typical example of this group of subjects.

Case 3:—A 73-year old colored man (W.D.) was admitted to the hospital in April, 1956. For 10 months he had been weak, complained of anorexia and had noted foamy, liquid stools, especially at night. His diet was poor and he had lost 30 pounds in weight. Examination revealed severe undernutrition and atrophic glossitis. The blood pressure was 110/50. Hemoglobin was 6.1 gm./100 ml.; erythrocyte count, 1.26 million cu. mm.; MCHC, 34 per cent and MCV, 142 cu. μ. The bone marrow was megaloblastic. Free acid was present in the gastric juice after histamine stimulation. The stools contained large amounts of fat and fatty acid crystals. The level of calcium in the serum was 6.2 mg./100 ml.; that of phosphorus, 3.1 mg./100 ml. Serum albumin was 2.9 gm./100 ml.; globulin, 1.9 gm./100 ml. A glucose tolerance test was normal (Table I) as were tests of liver function. The level of carotene in the serum was 68 μg/100 ml. and the Vitamin A tolerance curve was flat. X-rays of the small bowel showed no abnormalities. A malabsorption pattern was observed with the Schilling test. An excellent response followed therapy with Vitamin B_{12} and this response has been maintained with 1 mg. of the vitamin once weekly by mouth.

Comment

Most of the 21 subjects who were found to have malabsorption of Vitamin B_{12} had evidence of malabsorption of other nutrients as well. In some instances there was diminished absorption of all substances tested, in others the absorptive defect involved only one or two materials. Of the seven patients in whom fat balance studies were carried out, only one had completely normal absorption

of fat i.e. over 95 per cent. Two others, however, absorbed 90 and 92 per cent of the fat ingested. Two subjects with malabsorption of fat appeared to absorb Vitamin A normally.

Serum Vitamin B_{12} was low in each of the 11 subjects in whom it was measured during hematologic relapse, attesting to the deficiency of this vitamin. Studies of folic acid absorption were not carried out in these subjects. Chanarin and associates[10] have observed diminished absorption of folic acid in patients in whom clinical and laboratory findings were similar to those reported here. In the current study, some patients were treated with folic acid on one occasion and with Vitamin B_{12} on another. They seemed to respond equally well to either vitamin from both a clinical and hematologic standpoint.

Treatment with folic acid or Vitamin B_{12} did not result in completely normal absorption of fat or glucose. Most of the fat balance studies and some of the glucose tolerance tests were carried out after the blood count had returned to normal and the patient's general condition had improved markedly. In spite of the persistence of absorptive abnormalities, the patients were free of symptoms and appeared to be in good nutritional condition. Similar findings have been observed by others in studies of the sprue syndrome. Improvement in absorption of both glucose and fat have been reported in many instances even though normalcy may not be attained.

Malabsorption of Vitamin B_{12} has persisted in the patients reported here. In most instances, the malabsorption was detected by the Schilling test during clinical remission. Relapse has occurred in several subjects when therapy with Vitamin B_{12} was discontinued. In some patients with sprue syndrome absorption of Vitamin B_{12} is normal. We have observed this in several instances.

The cause of the absorptive defect in this syndrome is not understood. In patients with nontropical sprue, many of whom resemble those described above, improvement has followed administration of a gluten-free diet. It has been suggested that the malabsorption syndrome represents an inborn error of metabolism[11]. Even if this proves to be the case, the role of Vitamin B_{12} or folic acid is far from clear nor can the efficacy of the gluten-free diet be explained adequately. It is difficult to understand why a metabolic error does not result in serious symptomatology until late in life. The precipitating factors in the syndrome likewise are vague. Anorexia and intercurrent infection preceded the development of macrocytic anemia in a number of the patients in this series. Histologic changes have been observed in biopsy specimens of the intestinal mucosa in the sprue syndrome with a return toward normal following therapy with Vitamin B_{12}, folic acid or both vitamins[12]. The cause of these changes remains unknown.

It may be that the malabsorption syndrome includes more than one distinct entity. In studies of the etiology of macrocytic anemias in our laboratory, we

have found that some patients with the malabsorption syndrome appear to have a lower than normal amount of intrinsic factor in the gastric juice[13]. Other subjects seem to have a decrease in the amount of receptor protein in serum that binds Vitamin B_{12}. *In vitro* studies by Miller and associates[14] indicate that intrinsic factor stimulates the binding of Vitamn B_{12} by serum and tissue proteins and that a co-factor is required for this reaction. Perhaps deficiency of this co-factor is related to the malabsorption of Vitamin B_{12} in some subjects.

In this study, most of the subjects were treated with large oral doses of Vitamin B_{12}. Such therapy has been found to be effective in pernicious anemia, and was equally satisfactory in these patients. Large amounts of Vitamin B_{12} appear to be absorbed by a mechanism that differs from that for small quantities[15]. In this series, Vitamin B_{12} has been administered in amounts of 1 to 3 mg. once weekly and has proved satisfactory for maintenance of hematologic remission without the addition of folic acid. The latter vitamin in doses of 5 mg. daily has also maintained hematologic remission in a number of subjects. Some patients receiving folic acid, however, have improved when Vitamin B_{12} was added to the therapeutic regimen.

The frequency of the malabsorption syndrome in patients whose presenting complaints were due to macrocytic anemia was unexpected. One-third of these patients were considered to be pernicious anemia and one-third nutritional macrocytic anemia from the standpoint of clinical diagnosis when they were first examined. The true nature of this disorder would not have been discovered without the use of a test which measured Vitamin B_{12} absorption.

Summary

Twenty-one patients whose outstanding feature was macrocytic anemia were found to have malabsorption of Vitamin B_{12} not corrected by administration of intrinsic factor. Evidence of Vitamin B_{12} deficiency included anorexia, weight loss, glossitis, macrocytic anemia with a megaloblastic bone marrow, paresthesias of the hands and feet, low concentration of Vitamin B_{12} in serum and response to therapy with this vitamin. Malabsorption of Vitamin B_{12} may be a permanent defect as it has persisted after satisfactory response to therapy and relapse has occurred in the several subjects in whom treatment was discontinued. In this syndrome, the sole absorptive defect may be for Vitamin B_{12} (and perhaps folic acid) but usually there is decreased absorption of one or more other nutrients including glucose, fat and fat soluble vitamins. Therapy with Vitamin B_{12} results not only in hematologic remission but also in restoration of a good state of nutritional health even though absorptive defects of several nutrients may persist. Patients with this syndrome have improved with administration of folic acids as well as with Vitamin B_{12}. The primary etiology of this malabsorption syndrome is unknown. Certain factors that may be important in the pathogenesis are discussed.

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DISCUSSION

Dr. O. H. Wangensteen:—Inasmuch as you have called on me, I will rise to say how much I enjoyed Dr. Goldsmith's nice paper. I wish I could give a paper as well as Dr. Goldsmith does. A lot of progress has been made in the field. I should like to add too what a wonderful group of papers we have had from the New Orleans' contingent.

Dr. Goldsmith said nothing about gastric resection. We all know of the macrocytic anemias that attend total gastrectomy, but which respond to Vitamin

B_{12} as does the megaloblastic anemia of pernicious anemia. I would like to ask Dr. Goldsmith what experience she has had with distal extensive but subtotal excision of the stomach in man and the anemia problem.

During the past few years, some publications have appeared in the English literature that affect to cast doubt on the existence of an intrinsic factor. Can you tell us something about all this?

In January of this year, I had the great privilege of talking with George Whipple of Rochester, N. Y. He has retired from the Deanship but continues to prosecute a very interesting research program. He is indeed a very stimulating man, who has done so much in this important area of research. While we talked, Dr. Whipple drew out from his desk a large sheet of paper on which he kept his data on experiments which he was doing on the deposition of radioactive Vitamin B_{12} given to dogs. After a period of time, the dogs were killed and Dr. Whipple examined the various organs of the body with a Geiger counter to assess Vitamin B_{12} deposition. He said to me: "In which tissue of the body would you anticipate finding the greatest deposition of Vitamin B_{12}?"

I said, and I suspect most of you would think the same, "Why, in the gastric mucosa, of course."

He said, "No, you are wrong. It is greatest in the heart muscle; that occurrence must have some meaning." And I suppose it does.

He continued, "Second in the brain; third in the gastric mucosa; and next in the liver."

It is a romantic and wonderful field in which to work, and I think many important discoveries remain to be made. My colleagues, Drs. P. A. Salmon and W. O. Griffen, Jr., and I have noted that a number of our achlorhydric patients who have gastric cancer are not apeptic. In other words, achlorhydria and apepsia are not synonymous. Is it the apeptic achlorhydric patient who is likely to develop megaloblastic anemia? Certainly the patient who has pernicious anemia has apepsia, as well as achlorhydria.

Dr. I. Snapper:—We have to be grateful to Dr. Goldsmith because she has obtained results which indicate that the pathogenesis of pernicious anemia is not as simple as we nowadays wish to believe.

The absence of intrinsic factor which prevents the absorption of Vitamin B_{12} from the intestine does not explain why folic acid improves the hematologic changes in pernicious anemia but deteriorates the neurological condition.

It is also remarkable that tropical nutritional anemia which is improved by marmite, an extract of yeast, and peroral liver administration, does not react favorably when purified liver extracts are injected. The interesting results of

Dr. Goldsmith indicate which methods must be used to approach these important problems.

Dr. Grace A. Goldsmith:—I want to thank Dr. Wangensteen and Dr. Snapper for some very interesting comments relative to this kind of anemia, and for discussing the macrocytic anemia which follows gastrectomy and even partial gastrectomy. We have had a number of these patients and in most instances in which macrocytic anemia has developed, the Schilling test has indicated an absence of intrinsic factor rather than the type of malabsorption syndrome presented here.

Relative to some of the work which was mentioned in which some English investigators claimed that perhaps our whole concept of intrinsic factor may be wrong, it is my opinion that the findings presented by these workers can be explained in many other ways. Furthermore, I think we have very excellent evidence for the essentiality of intrinsic factor in the absorption of Vitamin B_{12}. Then there is a second type of malabsorption of Vitamin B_{12} in which some other defect is present.

Intrinsic factor doesn't do anything in this syndrome. Why don't these subjects absorb Vitamin B_{12}? This is a question to which we do not have the answer as yet and one which needs a great deal more study.

EPIDEMIC NONICTERIC VIRAL HEPATITIS*

A Report of 120 Cases

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The problem of viral hepatitis is growing in clinical and public health importance. Although its jaundiced form is the obvious expression of this disease, the nonjaundiced form of viral hepatitis is now being recognized as responsible for as much as 70 to 80 per cent of all cases[1,2]. It is this variety of viral hepatitis that is still largely an unrecognized clinical entity and is probably responsible for many avoidable or unrecognized complications of the disease which practicing physicians encounter.

This report deals with 120 demonstrated cases of nonjaundiced forms of viral hepatitis. A previous report by the authors described observations during a recent epidemic of the jaundiced type in a Southern California college.[3]

In November of 1956, the Los Angeles City Health Department officially reported an outbreak of several hundred cases of the icteric form of viral hepatitis in West Los Angeles[13]. The source was traced by city health officers to a trailer camp and was the result of water contamination in this area.

At this same time, the authors became aware of an outbreak of illness which presented a "flu-like" syndrome without jaundice, but with either an enlarged or tender liver to abdominal palpation. The symptoms resembled those of a mild or moderate bout of influenza; the complication that developed, however, was that it coincided with the incidence of an endemic outbreak of so-called "Asiatic influenza" and other milder resemblances to the disease.

One of the main contributory difficulties to the clinician's problems in diagnosing viral hepatitis has been the well-known absence up to now of any diagnostic test for viral hepatitis. This objection has recently been met as reported by the authors who have introduced a new hemagglutination test for viral hepatitis[4,5]. This test has been shown to have some specificity for the virus of viral hepatitis and its use has been recently confirmed by various investigators[6,7]. Kuhns has already used the h.a.t. for viral hepatitis in screening 7,332 blood donors at a University Blood Bank Center[7]. The test is also

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now in use at various other medical centers or university blood banks as a "screening" procedure. To date, the authors have employed the test in over 2,000 patients and blood donors and found that it has a higher diagnostic accuracy in viral hepatitis than the commonly used liver function tests for this disease such as the thymol turbidity and the cephalin flocculation tests[8].

The hemagglutination test (hereafter referred to as the h.a.t.) for viral hepatitis used *M. rhesus* erythrocytes which are agglutinated in the blood serum of patients with viral hepatitis. Hemagglutination reactions have been found to occur in influenza, where the virus agglutinates fowl erythrocytes, and in infectious mononucleosis, where sheep red cells are agglutinated by the patient's serum.

In the following study, these 120 patients were referred by a group of physicians in the affected area. All patients had their histories taken and physical examinations were performed. In addition, the blood of each patient was tested with thymol turbidity and cephalin flocculation liver function tests and the h.a.t. for viral hepatitis. Complete blood counts and urinalysis were performed routinely; the heterophile reaction was performed in many cases as well as serological tests for syphilis, serum bilirubin and icteric index.

Clinical Material

The blood serum of patients tested for viral hepatitis was collected through hospital laboratories. Patients suspected as affected by viral hepatitis presented symptoms usually associated with the clinical picture of influenza, such as fever, malaise, generalized aching, arthralgia, cough, sore throat, abdominal pains, nausea with vomiting or gastrointestinal upset, and occasional diarrhea. In the great majority of cases (92 per cent) (in our series of 120 thoroughly studied patients) the liver was either palpable and/or tender. This was the only significant physical finding common to almost all of these cases and agrees with the same findings reported by other authors[1,2].

No visibly jaundiced patients or patients with elevated serum bilirubin were included in this series. Only a small number of these patients were in direct known contact with other patients suffering from acute viral hepatitis.

The ages of patients ranged from 9 to 68 years of age; 78 were females and 42 were males. The preponderance of females in some epidemics of viral hepatitis has been noted by some authors[9,15], 114 or 95 per cent of the patients were treated throughout their illness at home or in the physician's office and only 6 patients required hospital care or complete bed rest.

The majority of patients were advised to follow a nutritious well-balanced diet with no fat restrictions and were given palliative medication, analgesics, and vitamin supplements. A small number were given oral or parenteral antibiotic therapy.

The liver was found to be enlarged from one to three fingers breadth in 73 or 61 per cent of the cases. The liver was tender or painful to deep abdominal palpation in 108 or 90 per cent of cases during the acute onset of the illness. The spleen was enlarged or palpable in 4 cases. The duration of illness in patients who did not suffer relapse or develop persistent symptoms was from one to four weeks with an average of two weeks before complete disappearance of symptoms. Relapsing patients will be discussed later.

Our five criteria for the diagnosis of anicteric viral hepatitis in the 120 patients were: 1. Symptoms of influenza, a "cold", or respiratory infection; 2. Palpable, enlarged or tender liver; 3. Positive h.a.t. for viral hepatitis; 4. positive thymol turbidity liver function test and 5. Positive cephalin flocculation test.

In addition to the 120 carefully studied cases described in this paper, there were 92 additional highly suspect cases referred by various other physicians. These patients are not included in this study because more than one of our five necessary diagnostic criteria for nonicteric viral hepatitis was absent. Regarding these five essential requirements, some of these cases which were excluded may have had 1. a thymol turbidity liver function test done, but not 2. a cephalin flocculation test or vice-versa. Others may have had both these liver function tests completed but 3. careful palpation for an enlarged or tender liver was not made.

All of these 92 cases, however, 4. were tested for the h.a.t. for viral hepatitis and 5. presented the same clinical picture as described for the 120 patients described above with the flu-like syndrome. The analysis of results in the 92 cases not reported however were very similar to those described in Table I for the 120 reported cases.

Methods

The h.a.t. for viral hepatitis employed in this study was essentially the same as that described by the authors in previous publications[4,5] with some modifications as follows:

Twofold serial dilutions of the patient's serum are made to which are added equal volumes of a 2 per cent suspension of red blood cells obtained from a Macacus (*M. rhesus*) monkey. The red blood cells are stored in A.C.D. solution. When ready to be used it is incubated for one hour in a 37°C. water bath. At the end of this time, the tubes are placed in a centrifuge and spun at 500 r.p.m. for two minutes. The tubes are shaken gently to dislodge the button of sedimented erythrocytes and the cells are examined by transmitted light for the presence of clumping.

In a negative test the cells can be resuspended by gentle agitation into a smooth homogeneous suspension. A positive reaction is indicated by the presence of small to large clumps of cells in the fluid medium. In cases of doubtful positive reactions it was found that repeating the reading in 20 to 30 minutes

will often eliminate false or doubtful positive reactions. The conventional scoring is used in the readings and is described below:

4+ . . . . The cells are welded into one or two solid masses;

3+ . . . . Several large, irregular clumps with numerous smaller aggregates;

2+ . . . . Moderately large clumps, uniform in size and distribution;

1+ . . . . A granular appearance due to the presence of small clumps of cells;

± . . . . Very finely granular appearance due to the presence of minute clumps of cells. This tube is read in comparison with the cell control and may be confirmed by microscopic examination when necessary.

In testing a series of 125 healthy blood donors[4], our observations led us to fix the value of 1:8 as the titer which separates normal from elevated readings. The findings reported subsequently support this concept[3,5].

Readings of 1+ in 1:8 dilution should be rechecked at 5 or 30-minute intervals, if necessary, to distinguish between true agglutination and nonspecific granularity observed with certain cell suspensions. The granular cells tend to go into a smooth homogenous suspension on standing, while in true agglutination, the clumping remains constant.

The thymol turdibity test was employed as introduced by MacLagan[10]. The cephalin flocculation test used is that of Hanger[11] as modified by Shank and Hoagland[12].

Results

Analysis of the history and physical examination for characteristic findings reveals only nonspecific presenting symptoms of the "flu"-like syndrome for the former, and an enlarged or tender liver for the latter. These findings in both the history and the physical examination were almost identical with two exceptions to those found in the outbreak of 368 cases of jaundiced viral hepatitis reported by the Los Angeles City Health Department[13]. The differences were that in the anicteric form of the hepatitis the symptoms were milder in general and of shorter duration. These observations have also been noted by other investigators[1,2].

Table I consists only of 120 nonjaundiced patients with 1. influenza-like symptoms and 2. either an enlarged or tender liver to abdominal palpation. These cases occurred at the time and in the area of the reported epidemic of jaundiced viral hepatitis as described above. They were therefore suspected as cases of nonjaundiced viral hepatitis and were tested with the h.a.t., thymol turbidity and cephalin flocculation liver function tests for viral hepatitis.

In our series scarcely any infants or children were studied. As has been pointed out by Capps et al[16], this is probably due to the general consideration that infectious hepatitis is regarded as rare in the very young[17].

In over 20 cases, a complete liver function test battery was performed, including thymol turbidity, cephalin-cholesterol-flocculation, quantitative and qualitative urobilinogen, total serum bilirubin, alkaline phosphatase, cholesterol-esters, prothrombin time, serum albumin globulin, and bromsulfalein dye retention. It was found that such a liver "profile" did not contribute anything of significance over and above the simple performance of the thymol turbidity and cephalin flocculation tests. These latter were then adopted routinely in all cases studied, as shown in Table I. Normal values for thymol turbidity tests were from 1 to 4 units[10]. Normal values for the cephalin-cholesterol test were 1+ and 2+ reactions at 24- and 48-hour readings[11].

It is noted (Table I) that the h.a.t. was positive in 78 or 65 per cent of patients with influenza-like clinical pictures. The thymol turbidity test was positive in 46 cases or 38 per cent. The cephalin flocculation test was positive in 61 cases or 51 per cent of patients.

TABLE I

NONJAUNDICED CASES OF VIRAL HEPATITIS WITH FLU-LIKE SYMPTOMS

Number of cases.	Enlarged and/or tender liver.		Positive hemagglutination test for viral hepatitis.	Positive cephalin floc. test.	Positive thymol turbidity test.	Positive correlation of hemagglutination test with both liver function tests.	Positive correlation of hemagglutination test with one liver function test.
	Enlgd.	Ten.					
120	73 (61%)	108 (90%)	78 (65%)	61 (51%)	46 (38%)	74 (62%)	94 (78%)

The h.a.t. gave more positive reactions than one or both the liver function tests in 17 cases of viral hepatitis. Control cases are run simultaneously with each batch of sera tested, there being at least 10 to 20 controls of diseases other than viral hepatitis determined at every testing period.

It is therefore noted that although 78 (65 per cent) out of 120 cases of the studied cases were positive for the h.a.t., 12 additional cases were weak positives. Since these studies were initiated it is possible that improvements in technic now in adoption may have converted these "doubtful" positives into more definite reactions.

Comparison of the thymol turbidity with the cephalin flocculation tests in this epidemic reveals that the former was 13 per cent less frequently positive than the latter. The cephalin flocculation test in turn was 14 per cent less frequently positive than the hemagglutination test. The cephalin flocculation test, however, gave a better correlation with the h.a.t. than the thymol turbidity test. It was interesting to note that in every case tested, with one exception,

when the thymol turbidity test was positive the cephalin flocculation test was strongly positive. Of the cases with positive cephalin flocculation tests, 13 per cent gave negative thymol turbidity reactions although the h.a.t. was positive in each case whenever the cephalin flocculation reaction was positive. Fifteen clinical relapses or 12 per cent occurred from one to five months after the acute onset of the illness. During these relapses all the original liver function tests and the h.a.t. became or remained positive.

Twenty-two cases or 18 per cent gave a positive heterophil reaction for infectious mononucleosis. Since the original technic, the h.a.t. has been improved to the extent that subsequent cases have shown a trend to reduce the number of positive h.a.t. in infectious mononucleosis cases. Previous observers have noted that up to 22 per cent of anicteric viral hepatitis cases gave positive heterophil antibody reactions[30,37]. These positive antibody tests were found to be normal-Forssman in type by Leibowitz[30] and by Denber[9] when absorbed with guinea pig kidney and beef cell antigen suspension.

No fatalities occurred in this group. None to date has become jaundiced to the authors' knowledge.

Comment

These studies emphasize the need for greater awareness of the prevalence of the nonjaundiced form of viral hepatitis. The new hemagglutination test for viral hepatitis can be of great clinical value in the detection of both the jaundiced and nonjaundiced forms of viral hepatitis. Our studies further draw attention to previous estimates that up to 70-80 per cent of viral hepatitis cases may occur in a nonjaundiced form[1,2].

During epidemics of icteric viral hepatitis physicians should be especially alert to the symptoms or clinical pictures suggestive of the forms of nonjaundiced hepatitis. Such symptoms as fatigue, malaise, chills, and/or fever, generalized aching, arthralgia, sore throat, a "cold", gastrointestinal symptoms such as anorexia, nausea, diarrhea should especially arouse the clinical index of suspicion for this disease. Abdominal pains or a palpable, tender liver in addition to the above symptoms should require the performance of liver function tests such as the cephalin-cholesterol flocculation test, the thymol turbidity test, and if at all possible, the hemagglutination test for viral hepatitis. These latter tests may not be positive in 100 per cent of cases as is also true of most other laboratory procedures; reliance, therefore, must also be placed upon clinical judgment based on the history and positive physical findings regarding the liver in suspected cases.

As has been reported previously[9] the authors have found the most important physical findings in acute anicteric viral hepatitis to be an enlarged, palpable or tender liver.

In our series of 120 cases this abnormal liver sign was present in 90 per cent of cases studied and examined carefully. We have found in most patients with the nonjaundiced variety of viral hepatitis that the attending physician has treated these patients as cases of a bad "cold" or influenza. The great majority of physicians did not complete an exmination for evidence of a palpable or tender liver.

A high index of suspicion should be directed towards cases with symptoms of a bad "cold" or influenza, occurring during epidemics of the jaundiced form of viral hepatitis. A significant number of these cases may be shown to be suffering from nonicteric viral hepatitis.

Relapses occurred in 15 cases or 12 per cent of patients. These figures are comparable to those reported by Neefe[35] who has found that from 15 to 25 per cent of viral hepatitis cases may suffer mild relapses upon too early resumption of activities. Most of these cases recover within one year. Five per cent, however, fail to recover within one year. In our series relapses occurred usually from one to four months after symptomatic recovery from the acute illness.

Of particular interest is a group of patients with symptoms giving the impression of a psychoneurosis. In this group of patients predominating symptoms were nervousness, great fatigue, insomnia, lack of mental concentration, and the open development of latent trends to emotional disorders. Oftentimes there were associated vague gastrointestinal symptoms. It has already been pointed out by other authors that psychosomatic complaints may be mimicked by nonicteric viral hepatitis[31].

The above observations were particularly emphasized in World War II where a large number of such cases occurred and were discharged from military service with a diagnosis of psychoneurosis[9,31]. Subsequent evaluation and studies frequently revealed that these servicemen were suffering from the chronic or relapsing form of recurrent nonicteric viral hepatitis.

The carrier state of the virus in this disease is of considerable public health importance. The transmission of the virus through carriers by blood and plasma transfusions or hypodermic needles and surgical instruments is too well-known to require comment. If blood is obtained at blood banks during epidemics of viral hepatitis, special attention should be directed to all blood donors for the possibility of detecting carrier states. Abdominal examination of prospective blood donors for a tender or palpable liver at such times should be routine. Wherever possible the hemagglutination test for viral hepatitis should be performed in conjunction with cephalin-flocculation and thymol turbidity tests. Positive cases should be screened as suspected viral hepatitis carriers wherever possible. Studies should be initiated to determine whether these suspected blood donor carriers are transmitting the virus to blood or plasma recipients. It is well known that the vast majority of these carriers are entirely symptom-free.

Reference should be made here to the reported increased incidence of cirrhosis of the liver as a complication of nonicteric viral hepatitis[32,33]. Some authors such as Bjorneboe[34] have reported a high and increased incidence of posthepatitis necrosis of the liver as a result of viral hepatitis. This is an additional example of striking individual variations to be seen as complications of this disease. We believe that there is a broad spectrum in these variations of complications, possibly due to different strains of the virus. MacLean[36] has already demonstrated the characteristics of some 48 different varieties of the virus of viral hepatitis in tissue cultures.

It is of particular interest to note that there were only 3 cases of children under 14 years of age tested or suspected of anicteric viral hepatitis in this series. Comparatively few cases in the very young have been reported. Concerning the occurrence of the nonicteric form of viral hepatitis in infants and small children, virtually nothing is known other than the fact that it does occur[16]. Several cases have been recognized occurring in association with the typical form of viral hepatitis in epidemics of this disease[18,19].

Webb et al[20] found nine nonicteric and six icteric cases in a group of children between one and three years of age, suggesting a higher incidence in the former.

As already pointed out[21,22] the reason for lack of recognition of viral hepatitis in the very young may be that only recently has viral hepatitis been recognized as a common clinical entity in adults. Other investigators have attributed this to a lack of a specific diagnostic method for the disease for both children and adults[16]. Most physicians regard viral hepatitis in children as mild, transient, and without complications or after-effects[23,24]. Despite this impression deaths[24,25,26], cirrhosis of the liver[27,28] and other sequela have been reported.

The hemagglutination test for viral hepatitis has indicated that with the exception of infectious mononucleosis, it may be developed as a specific test for viral hepatitis. Further modifications and refinements are under study to introduce the possibility of its routine use as a diagnostic and screening procedure for viral hepatitis. The test has already been described and confirmed by other investigators for these purposes[6,7]. Further studies along these lines have been initiated by the authors and will be reported subsequently.

Addendum

Since submission of this paper, additional confirmation of the hemagglutination reaction in viral hepatitis has recently appeared[38].

Summary and Conclusions

1. 120 cases of the nonjaundiced form of viral hepatitis were studied during an epidemic of icteric viral hepatitis.

2. All cases were diagnosed by the rhesus hemagglutination test for viral hepatitis, positive cephalin cholesterol flocculation, thymol turbidity tests and an enlarged or tender liver to abdominal palpation.

3. The nonicteric form of viral hepatitis in this series mimicked upper respiratory tract infections, a "cold", the influenza-like syndrome, or psychoneurosis.

4. Clinical relapses and the danger of posthepatitis complications or sequela in the nonicteric form of viral hepatitis are discussed.

5. Attention is drawn to the frequent occurrence of the nonjaundiced form of viral hepatitis during epidemics of icteric viral hepatitis. Particular awareness of this condition should result in palpation of the liver for enlargement or tenderness in all suspected patients who complain of a "cold" or vague generalized symptoms, or who may present the "flu"-like syndrome.

6. The carrier state of viral hepatitis is discussed with particular reference to blood and plasma transfusions.

7. The hemagglutination test for viral hepatitis was found to be a valuable screening and diagnostic test which may have specificity for both infectious and homologous serum varieties of viral hepatitis.

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MECKEL'S DIVERTICULUM*†

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Introduction

Meckel's diverticulum is an interesting intestinal anomaly that occurs in approximately 2 to 4 per cent of all cases coming to autopsy.

This diverticulum is a blind out-pouching, usually on the antimesenteric border of the terminal ileum. It is located 15 to 100 cm. from the ileocecal valve. Developmentally, this anomaly is due to failure of the omphalomesenteric (vitelline) duct to obliterate and become absorbed.

Historically, LaVater[1] in 1672 first mentioned its existence. Ruysch[2] (1701) published the first illustration of the ileal diverticulum; Littre[3] (1742) reported its presence in a hernia sac; and Meckel[4], for whom the anomaly is named, in 1809 and 1812 first accurately described the lesion and emphasized its embryological significance and clinical importance.

Incidence

Although Meckel's diverticulum is said to occur in 2 to 4 per cent of all cases coming to autopsy, the clinical incidence is considerably less. One single series on record is the 49 cases reported by Gross[4] in 1950, from the Boston Children's Hospital. Umphrey's[5] report is more typical. Over a five-year period at the Florence Crittendon Hospital in Detroit there were nine cases of Meckel's diverticulum in 3,406 abdominal operations. If, as Umphrey remarks, the incidence at autopsy is a minimum of 2 per cent, this means that out of an expected 69 diverticula at this institution, 60 were missed. This, he believes, is the usual average. Three of the nine patients had previously been operated upon without discovery, or at least removal of the diverticulum.

In our series, there were 129 cases of Meckel's diverticulum which occurred at Touro Infirmary and Charity Hospital in New Orleans from 1950 through 1956. These were all cases found at operation and were not autopsy cases.

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Sex and Age Distribution

Meckel's diverticulum is more frequent in males. In Gross'[4] series of cases in children, the male incidence was 75 per cent. In our 129 cases, there were 65 males and 64 females.

This condition may be found in any age group, although complications occur most often in children and young adults. The average age of our entire series was 25 years.

Race and Hospital Incidence

The racial and hospital incidence in our series is interesting. Touro Infirmary, 430 of whose 500 beds are private, had half as many cases in 6 years as occurred at Charity Hospital, with approximately 2,900 beds. This is not, however, a disease peculiar to any social or financial level.

At Charity Hospital, during this period, Negro admissions have exceeded white admissions by a ratio of approximately 70-30. In the 86 cases from this hospital, however, Meckel's diverticulum was found in Negroes only 26 times (30 per cent). In the Charity Hospital cases, the incidentally observed diverticula were identified at operations performed in the immediate vicinity of the ileum. In the Touro Infirmary cases, many of the operations were performed on remote strictures, such as the stomach, gallbladder, and colon.

Diagnosis

The diagnosis of Meckel's diverticulum is difficult to make preoperatively. In only two cases in this series did the diverticulum visualize in a barium gastrointestinal series.

In certain clinical situations, the high probability of the diagnosis is evident. For example, in massive gastrointestinal hemorrhage in infants and small children the most probable diagnosis is Meckel's diverticulum. The same is true in cases of obstruction of the terminal ileum, in children or young adults, who have not had previous abdominal operations.

The occurrence of an acute inflammatory process in the lower right abdominal quadrant, if the appendix was previously removed, would suggest an overlooked Meckel's diverticulum.

This anomaly can be overlooked, even if deliberately sought, in one of two ways. One is failure to continue the exploration far enough up the bowel. Meckel's diverticulum has been found as far as three feet above the ileocecal valve, and occasionally higher[8]. The other explanation is that the diverticulum is occasionally present on the antimesenteric border and may be easily overlooked.

Complications and Treatment

There were seven cases in this series in which bleeding was the indication for surgery. The ages of these patients varied from 6 months to 25 years—the average age being 9 months.

The hemorrhage was massive in four cases and presented as maroon colored blood in the stools. Pain was usually absent or only slight.

The explanation of all bleeding in Meckel's diverticulum is the presence of gastric mucosa which causes peptic ulceration[7]. Gastric mucosa was identified microscopically in six of the seven cases of hemorrhage in this series.

In the two cases of hemorrhage, in which intestinal resection was performed, the peptic ulcerations were definitely identified. In the other four cases, in which only diverticulectomy was done, the ulcers were not definitely identified—undoubtedly being present in the adjacent ileum.

There were 13 cases of acute diverticulitis. These all resembled acute appendicitis, except that the localization was not infrequently in the lower mid or lower left abdomen. Gangrene and perforation may follow suppuration, just as in acute appendicitis. There were two perforations in this series, one of which was caused by a fish bone. Waldron has experienced a similar fish bone perforation[8].

Intussusception of the Meckel's diverticulum caused obstruction in one of the 12 cases of obstruction in this series. In seven cases, the obstruction was caused by volvulus of the adjacent bowel, as the result of fixation by a congenital peritoneal band. In three cases, one of them a giant diverticulum, the bowel was kinked by adhesions. In the remaining case the diverticulum and the adjacent ileum had undergone strangulation in the sac of an inguinal hernia (Littre's hernia).

In one case, a 6-week old infant, the diverticulum was contained in, and connected with, a small omphalocele. The abdominal wall defect was repaired but the diverticulum was not removed.

In none of the 82 cases in which operation was done for either acute or chronic pain was there any evidence of other pathology in the abdomen. Gastric mucosa was found in seven of these, but there was no evidence of bleeding.

Pain in such cases is probably due either to recurrent attacks of mild diverticulitis or to recurrent attacks of incomplete obstruction.

Most surgeons agree that removal of the diverticulum is justified in such cases, even though there is no definite evidence of pathology. The high percentage of patients who have no further trouble justifies this policy.

Incidental removal of a Meckel's diverticulum, when other pathology is present, is indicated if the patient's general condition is not jeopardized by

extending the operative procedure. Such was the situation in 36 cases in this series.

In four cases, the diverticulum was found and not removed. One was in an omphalocele and two others in infants with inguinal hernias. In the fourth case, the diverticulum was not removed at hysterectomy because it was quite short and had a very wide base. This situation would have necessitated intestinal resection.

In general, we believe that Meckel's diverticulum should be removed because of the possibility of complications at almost any age.

There was no instance of failure to recognize the diverticulum as the source of symptoms in the acute cases in this series. A number of such instances are reported in the literature[9], the majority of them fatal.

Mortality

In this series, there was only one death. This occurred in an 11-year old white child operated on at Charity Hospital because of recurrent abdominal pain and a recent attack of four days' duration, suggestive of atypical appendicitis.

At operation, the appendix was normal and a nonpathological Meckel's diverticulum was removed. Ileus during the postoperative period was controlled with a Miller-Abbott tube.

The child was brought back to the hospital a month later, desperately ill from an intestinal obstruction of seven days' duration. Exploration revealed a gangrenous and perforated ileoileal intussusception, precipitated by a three-layered sutured line at the base of the diverticulum[10]. Death occurred several hours following operation.

Giant Diverticulum

A giant Meckel's diverticulum was observed in this series in a 19-year old male[10].

The patient had a life-time history of recurrent cramping abdominal pain, associated with nausea and vomiting. During the preceding year the attacks had become more frequent and more severe, but had responded to conservative treatment. The present attack, which was of the same character, was of 12 hours' duration when the patient was admitted to the hospital.

The abdomen was slightly distended and tympanitic. Peristalsis was decreased. Tenderness was generalized, but more marked in the lower abdomen where there was also some muscle spasm.

X-rays showed marked distention of the small intestine, with very little gas in the colon.

Exploratory laparotomy revealed the distal ileum to be obstructed by a large cystic mass measuring 17 cm. x 24 cm. x 4 cm. and later shown to contain one liter of ileal contents. It was considered to be either a giant Meckel's diverticulum or duplication of the ileum. The mass and adjacent bowel were resected and an end-to-end anastomosis performed.

Recovery was uneventful and there have been no further symptoms. The final pathological report was Meckel's diverticulum.

It was easy to reconstruct the patient's symptoms in this case. The ileum became obstructed proximally and distally by kinking. The diverticulum, as a result, became filled with ileal contents. Intermittent filling and emptying of the large sac produced recurrent attacks of obstruction. Similar giant diverticula have been reported by other observers.

Familial History

An interesting finding, in our series, was the occurrence of four cases of Meckel's diverticulum in the same family[10].

The cases occurred in two young women and in two siblings of one of the women. The mother of the children had a gangrenous diverticulum, and one of the children had obstruction from adhesions. The other two cases caused recurrent abdominal pain.

Since the condition is congenital, one might expect familial occurrence to be relatively frequent. To our knowledge, however, no such grouping of cases has been previously reported.

Summary

A series of 129 cases have been analyzed. These showed the usual complications of hemorrhage, obstruction, diverticulitis, and abdominal pain. There was one death in this series.

Included in this series are four familial cases, and one giant Meckel's diverticulum.

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Discussion

Dr. James Stewart (New Orleans, La.):—I should like to congratulate Dr. Michel on his excellent presentation of this most interesting series of cases.

The subject of Meckel's diverticulum is one which is discussed frequently in medical literature. In fact, a study of the English language medical writing reveals over 300 articles on the subject in the last ten years. In spite of this, diagnostic errors continue to be common, complications continue to plague us, and deaths from the complications continue to occur.

It is obvious that we need to learn more about Meckel's diverticulum, particularly about the diagnostic aspects. One approach to such learning, of course, is collection and study of large numbers of cases such as Dr. Michel has done.

In the Naval Service recently we became interested in the subject and collected 141 cases from naval facilities over a five-year period. These were unselected cases. The results of this study will be published in the near future, but I should like to show you a few slides from this material.

(Slide) It is important to bear in mind that Meckel's diverticulitis may occur by different mechanisms, just as acute appendicitis may arise by different mechanisms particularly in different age groups.

This slide illustrates the less common type of so-called Meckel's diverticulitis, that which is due to vascular changes primarily, which result in gangrene of the diverticulum.

(Slide) This is an example of the more common type of Meckel's diverticulitis which microscopically shows acute inflammatory infiltration throughout the wall of the diverticulum. This is true of the proximal portion of this

diverticulum. The distal portion has undergone secondary vascular change. In both of these cases just shown the signs and symptoms were indistinguishable from those generally associated with acute appendicitis.

(Slide) This is a polyp arising in a Meckel's diverticulum, a rare finding. This was composed of gastric mucosa and caused massive rectal bleeding requiring administration of 8 pints of blood prior to surgery. In this case, a preoperative diagnosis of Meckel's diverticulum was made by exclusion, as it usually is in cases of bleeding. The upper gastrointestinal tract was excluded as the site of the bleeding by aspiration of clear bile-stained fluid by gastric suction, and the distal colon was excluded by negative proctoscopic examination.

(Slide) This is another fairly uncommon one. This is the only instance in the series of x-ray demonstration of Meckel's diverticulum. This was a 14-year old dependent brought in by his parents because of being pale and worn out, and seldom taking part in any play. The initial hemoglobin was 4.5 gm. Diagnostic studies were not very helpful until this small bowel study was performed. At operation the large bilobed Meckel's diverticulum was found, and was removed by resecting a segment of ileum. A large active ulcer was present at the junction of the diverticulum and the ileum.

X-ray demonstration of these lesions is not easy. It seems that some element of obstruction is necessary, either of the ileum itself or of the diverticular stoma. This obstruction must be sufficient to cause filling and retention of air, fluid, or the contrast medium in the diverticulum. Even in the most carefully done small bowel series one rarely is able to find the uncomplicated Meckel's diverticulum.

In one of our other cases the operating surgeon did an appendectomy for acute appendicitis and left in place a fair-sized Meckel's diverticulum. During the postoperative period we sent the patient to the x-ray department and told them, "This patient has a Meckel's diverticulum. Find it." You can imagine the diligence of their search, but it was fruitless.

Meckel's diverticulum remains a diagnostic challenge for us all.

Dr. O. H. Wangensteen:—Recently, I heard of a Chicago surgeon who was so enamored of the antral role in gastric secretions and hypersecretion phenomenon in antral exclusion that, on finding a Meckel's diverticulum at operation, instead of taking it out, he removed the antrum of the stomach and left the Meckel's diverticulum. This is carrying a good thing a little far, I think. A year or more went by—I do not know exactly how long, but the surgeon made a point of it; eventually he had to take out the Meckel's diverticulum because of continued hemorrhage. Many surgeons, I am certain, have thought of the theoretical possibilities of such an undertaking, because in the presence of gastric mucosa ectopically located, the antrum already is, in a

sense, "excluded" from the ectopic gastric mucosa. The surgical attack, in such instances, as in others concerning a Meckel's diverticulum, must be made upon the diverticulum itself.

Dr. I. Snapper:—I heartily agree that the difficulties of the diagnosis of Meckel's diverticulum are very great. In a child with an intestinal hemorrhage the possibility of a Meckel's diverticulum must, of course, always be considered. In adults, however, where this diverticulum only rarely gives rise to medical or surgical complications, the diagnosis will usually be missed.

Dr. M. L. Michel:—I would like to again emphasize the mechanism of the obstructions caused by a Meckel's diverticulum.

In the 12 cases of obstruction in our series, intussuception was present in one case. In seven cases, the obstruction was caused by volvulus of the adjacent bowel, as the result of fixation by a congenital peritoneal band. In three cases, one of them the giant diverticulum, the bowel was kinked by adhesions. In the remaining case, the diverticulum and the adjacent ileum had undergone strangulation in the sac of an inguinal hernia (Littre's hernia).

PENETRATING WOUNDS OF THE ABDOMEN*

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Hemorrhage and peritonitis, one or both, account for the high mortality from penetrating wounds of the abdomen. There are many sources for hemorrhage: division of all sizes of blood vessels in the abdomen or its parietes, perforation of hollow organs having a rich blood supply, or laceration of vascular solid organs. Hemorrhage begins immediately upon wounding, and with massive hemorrhage the threat to life is immediate.

Peritonitis, in contrast, is an after-effect of wounding. It is the result of peritoneal contamination from visceral perforations: leakage of intestinal content, leakage of bile or leakage of urine. Although the escape of contaminating material often begins immediately upon wounding, time is required for a critical infection to become established. With its highly effective defenses the peritoneum can usually withstand a period of contamination which is reasonably brief, sometimes even though soiling is massive. Otherwise, prior to the advent of antibiotics all sizable perforations would have been fatal, whereas this was not the case at all. Rather, it is the enduring insult of continued leakage which the peritoneum cannot withstand, even with antibiotics. Therefore, it remains essential for laparotomy to be prompt so that all perforations can be found and closed and all leaks sealed at the earliest moment feasible. Both civilian and military experience support the conclusion that the mortality rate rises with each hour's delay prior to the surgical repair of intraabdominal perforations.

Unfortunately in many cases the patient cannot be taken to operation immediately upon arrival at the hospital. He is frequently in a state of circulatory collapse and restoration of an adequate circulation is essential if it is possible. Although shock from wounding and shock from peritoneal soiling contribute to circulatory collapse, intraabdominal hemorrhage is the central feature. If frank shock is present one may assume that 40 per cent or more of the total blood volume has been lost. Blood substitutes should be administered followed by whole blood as soon as it is available. The blood can be given rapidly, by way of large veins and under positive pressure if necessary, or intraarterially if desired. It is important to delay surgery until the blood volume has thus been restored. With moderate blood loss an hour or two of replacement therapy serves to return the systolic pressure to a level of 90 mm. of mercury or above.

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It it fails to do so, however, and the blood pressure is still at a shock level after two or more hours of energetic replacement, one had best conclude that internal hemorrhage is proceeding at such a rate that there is little choice or hope other than immediate laparotomy and a direct attempt to arrest the bleeding. In these situations the hazard is very great. An ample quantity of blood must be available at operation, and one must be prepared to administer it rapidly.

Since the severity of intraabdominal bleeding is often concealed, it is wise in dealing with any abdominal trauma to be prepared for more voluminous transfusion during operation than the patient's preoperative appearance might seem to indicate. The escape of a large amount of blood into the abdomen may serve to raise the intraabdominal pressure markedly, particularly if the musculature of the abdominal wall is in spasm so that the abdominal cavity can hardly expand. As blood pressure falls this increased intraabdominal tension may serve to stem the hemorrhage to a considerable extent. After the systolic pressure has been partially restored, however, the bleeding may resume; particularly, the opening of the abdomen at operation, since it suddenly lowers intraabdominal pressure to atmospheric, often serves to dislodge clots and to precipitate renewed rapid bleeding.

The rule for management of open wounds of the abdomen can be contrasted with that for managing closed or nonpenetrating wounds. In the case of blunt trauma one usually has no reliable measurement of the violence of the blow received, while it is common knowledge that many severe blows as well as innumerable lesser blows over the abdomen cause no injury whatever. Consequently there is no reasonable approach to the management of blunt traumata other than to consider each case individually and to operate if and when there are signs of internal injury. As long as such signs are not apparent conservative treatment is indicated, but with continued observation. When systemic evidence of internal hemorrhage is detected, or if local tenderness and muscle guard appear to indicate peritoneal irritation, exploration is immediately in order.

In contrast to blunt traumata, penetrating wounds are externally visible, and with visible penetrations over the peritoneal cavity experience has shown the great likelihood of visceral injury. Therefore, in patients with visible penetrating wounds, exploratory laparotomy is mandatory unless the surgeon can demonstrate to his own satisfaction that the tract of the offending missile or instrument stops short of the peritoneal cavity. Such demonstration is possible in certain superficial tangential wounds, and in instances in which a single missile or a known number of missiles have penetrated the skin only to lodge in the subcutaneous layer or in the muscle layer, from which they can be removed locally. Otherwise, an exploratory laparotomy with negative findings carries such slight risk relative to the hazard of an overlooked perforation that prompt laparotomy must be the rule. Delay is permissible only in exceptional instances of multiple injury, as when treatment of trauma to the brain, to the

spinal cord or to the respiratory mechanism takes precedence, or when such extraabdominal injuries render anesthesia and abdominal surgery so hazardous as to justify delaying operation at a calculated risk.

Comparison of Civilian Wounds and Battle Wounds

In several respects the open wounds of the abdomen encountered in civilian practice differ materially from those seen as a result of battle action in modern war (Table I). In civilian practice 5 per cent or less of abdominal wounds are from miscellaneous objects causing penetration, as in traffic accidents, with the remaining 95 per cent or more being stab wounds or wounds by gunshot. In many series the stab wounds outnumber the gunshot wounds. The proportions, however, vary greatly, depending upon racial distributions and upon the area reporting. For example, in a report from the John Sealy Hospital, Galveston,

TABLE I

The Causative Agent in Penetrating Wounds of the Abdomen

A. *Civilian Wounds*	*Stab*	*Gunshot*	*Misc.*
3 civilian hospitals	45 to 78%	53 to 20%	2%
B. *War Wounds*	*Stab Wounds*	*Small Arms Fire*	*Fragmentation Missiles*
World War II	less than 1%	27%	72%
Korean Conflict		23%	76%

covering the decade 1931-1941, stab wounds slightly outnumbered gunshot wounds in the ratio of 53 to 47[1]. Sixty-two per cent of all wounded individuals were Negroes, that race then comprising 32 per cent of hospital admissions. Negroes suffered 80 per cent of the stab wounds and 54 per cent of the gunshot wounds. In turn, a 1947-1958 series from the same hospital which has just been compiled reveals that during this later period stab wounds have outnumbered gunshot wounds in the ratio of 2 to 1. Sixty per cent of all wounded individuals have been Negroes, who still constitute 32 per cent of hospital admissions. A smaller but quite significant Latin American element in the population has of necessity been included with the Anglo-American in both of these series, since all white patients are coded together by our Record Room.

In comparison, a 1950-1956 series reported from the city-county hospital at San Antonio, Texas, a city having a large Latin American population, showed that 78 per cent of the wounds seen at that hospital were stab wounds and only 20 per cent were by gunshot[2]. Almost 80 per cent of all wounded individuals

were Latin American, whereas their race counted slightly less than 40 per cent of the local population. Negroes, who numbered 7 per cent of the population, accounted for 15 per cent of the wounded. The average median age group of the entire series of 311 abdominal wounds was 18.8 years, revealing the problem with juvenile delinquency in that city.

Whereas these Galveston and San Antonio series indicate that the knife is the favored weapon in Texas, Loria, in 1948[3], reported that of 3,117 penetrating wounds of the abdomen treated during a 47-year period at the Charity Hospital of Louisiana in New Orleans, gunshot wounds outnumbered stab wounds in the ratio of approximately 54 to 46. Over 69 per cent of all penetrating wounds of the abdomen seen at the Charity Hospital had been suffered by Negroes.

In civilian hospitals the mortality rate of gunshot wounds is at least several times that of stab wounds. Intraabdominal injury from a stab wound is usually localized; widespread or multiple injuries are exceptional. Moreover, since many stab wounds are relatively superficial, exploratory laparotomy may reveal no serious visceral injury whatever in a third or more of cases.

In marked contrast to the civilian pattern, stab wounds by knife or bayonet comprise less than 1 per cent of the battle wounds of modern warfare. Although in training camps and in rear areas knife wounds may constitute a greater proportion of nonbattle injuries, on the battlefield 99 per cent of wounds are by small arms fire or by fragmentation missiles[4,5].

Small arms fire, i.e., by rifle, machine gun, pistol or rocket, caused 27 per cent of the battle wounds of World War II and 23 per cent of those of the Korean Conflict, while 72 and 76 per cent respectively were caused by fragmentation missiles, i.e., hand grenades, mortar and artillery shells, detonating land mines or exploding aerial bombs. Twice as many soldiers are killed in action by small arms fire as by fragmentation missiles, but since the latter agents wound three times as many soldiers, fragmentation wounds cause four times the morbidity of small arms fire and lead eventually to twice as many fatalities.

Although the abdomen comprises 11 per cent of the body surface, only 6 per cent of soldiers wounded in battle in World War II were wounded in the abdomen. This discrepancy must be related to the protection the soldier provides to his abdomen in assuming the crouching position, the abdominal wall thus offering a smaller target. Again, although 6 per cent of battlefield wounds were abdominal wounds, only 4 per cent of the wounds seen in Army hospitals were abdominal. This variance arose from the high battlefield mortality from wounds of the abdomen. The 6 per cent of the battle wounds which were abdominal accounted for 10 per cent of the soldiers killed in action; they caused another 15 per cent of deaths occurring after admission to a medical installation.

The closer a military hospital is to the front the greater the number of patients with abdominal wounds it will receive and the higher will be the mor-

tality figure, since a greater number having mortal injuries will survive to reach the hospital. Unless the hospital is close, however, there is greater delay between time of wounding and time of definitive treatment, so that there is increased risk to the wounded soldier. With the efficient ambulance services of modern cities the civilian hospital often has the advantage of receiving its wounded much sooner after injury. By the same token, a greater number of hopeless or moribund cases may survive to reach the civilian hospital and its mortality rates will be increased accordingly.

Actually it is difficult to compare the results in treating battle wounds of the abdomen with those in treating the penetrating wounds of civilian practice. The common stab wound of civil life is seldom seen in battle, while the preponderant wound of the battlefield, that of the fragmentation missile, is rarely encountered in civilian experience. Wounds by small arms fire are the only wounds in common. In this category, moreover, the muzzle velocities of the machine gun and army rifle so greatly exceed that of the traditional civilian revolver that the resulting wounds are comparable only because civilian shootings commonly take place at very close range*.

Historical Aspects

Although exploratory laparotomy has become the accepted treatment in cases of abdominal penetration, from the historical viewpoint laparotomy achieved no distinct success until relatively recent years. As one would expect with injuries in which critical hemorrhage is a common feature, not many patients could withstand anesthesia and major surgery until means became available for blood replacement. Improved methods for combating peritonitis were also essential to the recovery of many of those who did survive the initial surgery.

Until the latter part of the 19th Century surgical attack in treating gunshot wounds of the abdomen was limited to probing the tract for prognostic purposes and to attempt to locate the bullet, since great importance was attached to its removal. By 1882, however, J. Marion Sims had become the American leader in advocating treatment by open laparotomy[6]. Nevertheless, for a great many years the results with laparotomy were hardly better than those with nonoperative treatment. In 1887 T.S.K. Morton[7], reviewing the world literature, reported that 17 deaths had occurred in 22 laparotomies recorded for gunshot wound, a mortality rate exceeding 75 per cent. In laparotomy for stab wound 7 of 19 patients had died, a mortality of 37 per cent. Results reported in a symposium held at the 1887 meeting of the American Surgical Association were

*Although the military services supply data based upon the "killed in action", comparable information is rarely available in civil life, the mortality rates reported from civilian experience applying only to wounded who have survived sufficiently long for hospital admission.

scarcely better, whereas in the discussion at that meeting T. G. Richardson of New Orleans stated[8] that under a nonoperative regime at the Charity Hospital the death rate during the preceding five years had been 19 per cent in stab wounds of the abdomen and 60 per cent in wounds by gunshot, both figures being lower than those reported by Morton for treatment by laparotomy. Moreover, in 1888 the French surgeon, Reclus, published an amazing report of 66 recoveries without operation in 88 cases of revolver wound of the abdomen[9]. This recovery rate of 75 per cent with expectant treatment was never matched in other reports, and must surely have been related to the small caliber and low muzzle velocity of the French pistol of that day.

In spite of such reports, many prominent American and European surgeons continued to look upon laparotomy as an obligation in treating gunshot wounds, although during the decade 1890-1900 at the Charity Hospital the mortality rate was 68.9 per cent in 122 cases treated by laparotomy, but only 53.6 per cent in 120 cases treated nonoperatively[8]. Obviously, no significant lowering of mortality could be expected from laparotomy alone, in the absence of provision for blood replacement. Nevertheless, at the beginning of the Boer War in 1899 the British advised laparotomy when there were signs of intestinal injury. They then abandoned the practice when the death rate proved higher than with nonoperative management. The Boer rifles were of small caliber and possibly the intestinal mucosa plugged many perforations. Furthermore, according to Wallace[10] distances were so great in the South African War, and evacuation so interrupted, that when the wounded arrived at a surgical facility it was much too late for operation.

In view of this Boer War experience, during the early phases of World War I the British practiced the nonoperative management of abdominal penetrations. Missiles, however, were larger and more damaging and the mortality rate was excessive. Wallace estimated that of those soldiers who survived to reach a forward medical installation approximately 80 per cent died. Therefore, the practice of exploratory operation when feasible was reinstituted. With casualties operated upon at Clearing Stations nearer the front the results became significantly better. The mortality in those selected for operation averaged about 50 per cent. Correcting for the casualties classed as moribund, who were not subjected to operation, Wallace reported that mortality totaled 60 per cent among those reaching a medical installation, as compared to 80 per cent under the previous nonoperative plan[10]. Several reports from individual Clearing Stations published in 1916 and 1917 reported operative mortality rates ranging from 37.7 to 53.5 per cent[11-14]. Although operation was not undertaken in many of the most severely injured, one British surgeon remarked that surgical intervention in abdominal wounds proved "at least as profitable" as in gunshot fractures of the femur or in gunshot wounds of the skull. Saline was given subcutaneously or by proctoclysis but no mention was made of blood transfusion. Late in World War I, however, Robertson of the British Army did establish a

blood bank for supplying a transfusion service to Clearing Stations[15]; apparently this pilot endeavor came too late to effect a significant contribution.

During the years following World War I blood transfusion came into increasing use in civilian hospitals. The mortality rate in penetrating wounds of the abdomen remained high, however, often in excess of 50 per cent in the case of wounds by gunshot[12]. At the John Sealy Hospital in Galveston during the decade 1931 to 1941 we were able to maintain a somewhat lower rate, losing only 37.1 per cent of 35 laparotomies in patients who had been shot in the abdomen[1]. A series of 35 gunshot wounds, however, is somewhat small for statistical comparison, since a chance run of only 3 or 4 particularly severe injuries might change the over all result materially. During this same decade we lost only 10 per cent of 40 laparatomies for stab wound of the abdomen.

Although Robertson of the British Army had used dextrose to preserve blood in 1917, little came of the blood bank idea for nearly 20 years. In 1936 the Cook County Hospital in Chicago established the first blood bank in the United States. The Spanish Civil War and the approach of World War II gave great impetus to the use of preserved blood and to the creation of blood banks. There was also stimulated search for blood substitutes which would restore the blood volume more effectively than saline or dextrose solutions. Plasma, which proved to be the best, had the great advantages that it could be kept for a long period of time and did not require refrigerated storage.

In the meantime, the prevention of abdominal distention by Levin tube and Wangensteen suction had improved the prospects in peritonitis, as had the increased knowledge of fluid and electrolyte balances. The sulfonamide drugs were introduced in the late 1930's, and penicillin became available in 1944, in time for the Normandy invasion. Given these advantages and a well-organized surgical service, the results in World War II were revolutionary. With plasma available in forward stations and a supply of whole blood in all hospitals, with stores of sulfonamides and of penicillin, and with greater emphasis than ever before upon selection of qualified medical officers for positions of responsibility in surgery and in anesthesia, the wounded American soldier in the Mediterranean and European Theaters received a quality of surgical care never approached before in any battle area. This resulted in mortality rates slightly below 25 per cent in sizeable series of laparotomies for abdominal penetrations[16].

The Korean Conflict saw even further improvement. The plentiful supply of blood permitted resuscitation of some of the most severely wounded, while helicopter evacuation provided rapid transportation to a place for definitive surgery. Moreover, wide spectrum antibiotics were available in addition to penicillin. As a result of the innovations, during the latter phases in Korea the Surgical Research Team reported a mortality rate of only 12 per cent in laparotomies for battle wounds of the abdomen[4].

Results have improved similarly in civilian practice. A recent report from the Robert B. Green Memorial Hospital in San Antonio[3], covering the period 1950-1956, lists only 6 deaths in 243 laparotomies for stab wound of the abdomen, a mortality rate of 2.47 per cent, and 14 deaths in 64 laparotomies for gunshot wound, a mortality of 21.9 per cent. At the John Sealy Hospital in Galveston, during the 11-year period 1947-1958, we have lost 3 of 74 patients subjected to laparotomy for stab wound, a mortality rate of 4.1 per cent; however 2 of these 3 deaths were in patients who also had severe extraabdominal injuries. Over the same period we have had 4 deaths in 35 laparotomies for gunshot wound, a mortality of 11.4 per cent. This compares to a rate of 37.1 per cent in an equal series of 35 gunshot wounds we treated during the period 1931-1941. Thus, in less than 20 years, our death rate has decreased by more than two-thirds. This marked improvement, both in civil and in military experience, reflects the efficacy of blood replacement, and of the use of antibiotics.

Essentials of Management

In a majority of cases diagnosis of the presence of a penetrating wound of the abdomen offers no difficulty, inasmuch as the wound is seen on inspecting the abdominal wall. The possibility, however, of abdominal involvement when the wound of entrance is in another part of the body must always be kept in mind. Particularly to be suspected are wounds caused by missiles entering the chest, the back, the buttocks, the sacral region or the perineal area, and stab wounds of the back or of the lower half of the chest. Whereas x-ray pictures may be time-consuming and unnecessary when the wound is obviously abdominal, they play an important part in charting the course of a missile which has entered elsewhere but which may possibly have penetrated the abdominal cavity[17].

The first-aid treatment of abdominal penetrations consists of easing pain, combating shock, occasionally stemming hemorrhage by packing or pressure, applying a dressing, but with no effort to replace prolapsed viscera, and transporting the patient immediately to a place for definitive surgery. Antibiotic therapy is begun as soon as feasible and tetatnus prophylaxis is effected. A narcotic is administered, preferably by vein in the presence of shock, and nothing is permitted by mouth.

Immediately upon arrival at the hospital frequent charting of blood pressure, pulse rate and respiratory rate should be instituted, since subsequent changes in these vital signs will indicate the progress of shock therapy and will determine the best time for operation. As indicated at the beginning of this discussion, resuscitation by blood substitutes is followed by administration of whole blood as soon as possible. While the blood volume is being restored gastric suction is instituted, the essential history is taken, and a complete physical examination performed. The examination must include inspection of a

specimen of urine, obtained by catheter when necessary, to determine if hematuria is present. Digital rectal examination also is desirable; discovery of blood on the examining finger may point to a perforation of the colon in cases of stab wound of the back in which intraabdominal injury has not otherwise been established. In some situations the turning of the patient in order to examine the back and the buttocks presents a problem, and extensive wounds in these areas may require treatment prior to laparotomy in order to avoid turning the anesthetized patient onto his face after the abdominal operation.

As noted previously, failure of transfusion to restore an adequate systolic pressure within two hours ordinarily means persisting severe hemorrhage, and surgery to arrest bleeding should be undertaken, even in the presence of shock, if ample blood is available. On the other hand, in instances in which transfusion does restore the circulation satisfactorily, laparotomy should not be delayed further unless such delay is necessitated by some complicating factor. In a recently published volume dealing with abdominal surgery in World War II[16] Beecher emphasized the general experience that when systolic pressure had been restored to 80 mm. or above, and the pulse rate was falling, nothing of particular value was accomplished by further delay, wherefore it represented a waste of blood and plasma. Exception is intended, of course, when patients arrive so late that a septic peritonitis is already present, with distention, dehydration and electrolyte imbalance. In such cases a prolonged period of treatment and replacement is in order before the indications for surgery can be intelligently assessed.

Although the need for operative attention is urgent, abdominal penetrations do not necessarily hold first priority. An extraabdominal injury which embarrasses respiration or circulation frequently takes precedence. This is true of a number of thoracic penetrations and of certain injuries involving the brain or spinal cord. Until the cardiorespiratory mechanism has been stabilized, anesthesia and laparotomy carry particular risk.

The technical details of laparotomy for abdominal penetrations have been discussed in many places[17,18]. Since the present discussion has been directed particularly toward the broad problems of hemorrhage and peritonitis, only general points will be made in relation to operative procedure.

A plentiful supply of blood must be available in the operating room at time of surgery. Large gauge needles should be in place in two extremities, with infusions running. Exploration is facilitated greatly by endotracheal anesthesia, and also by a long abdominal incision which provides for wide exposure and ease of maneuver.

Upon opening the abdomen the first concern is the control of bleeding. If hemorrhage is massive rapid control is imperative. Laceration of the spleen necessitates splenectomy after ligation of its pedicle. Deep liver wounds which

bleed profusely are controlled by packing, at least temporarily. Bleeding omental and mesenteric vessels are ligated individually and accurately, proximal digital compression giving temporary control while clots are evacuated to permit precise visualization. Sometimes the delivery of the entire small intestine onto the abdominal wall aids in locating sites of bleeding along the mesentery or in the pelvis. In an occasional case serious hemorrhage arises from the epigastric vessels in the abdominal wall.

Although patients with major openings into the aorta or vena cava seldom survive to reach the surgeon, a retroperitoneal hematoma may point to a smaller opening which carries a lethal threat. Proximal and distal control by encircling tapes permits exploration of the aorta and the cava. If the retroperitoneal hemorrhage is found to arise from kidney injury, the surgeon should determine immediately whether an opposite kidney is present. Nephrectomy for hemorrhage, however, will be warranted only when the kidney or its blood supply is damaged irretrievably.

Once hemostasis is accomplished time is taken to prevent further gross spill from any larger gastrointestinal perforations which may have been noted during the search for bleeding. In many instances such openings can be isolated from the intestinal stream by noncrushing intestinal clamps, though in less accessible areas a suture may be necessary to occlude a perforation which is leaking freely. Multiple sites of profuse leakage from the small intestine may be cared for temporarily by exteriorizing the affected loops so that further spill will be external.

The next step is a thorough, systemic examination of the gastrointestinal tract from end to end. Particular attention must be paid to the posterior surfaces of the stomach and duodenum, and to the retroperitoneal portions of the colon, where injuries are easily overlooked. As exploration progresses all gross contaminating material encountered should be removed by suction or lifted away with a sponge. Most surgeons avoid extensive irrigation of the peritoneum in the belief that it acts to disseminate contamination.

Perforations of the stomach and duodenum are closed accurately and securely. Drainage will be indicated in cases of injury to the duodenum or pancreas involving the retroperitoneal tissues, and drains will also be required when there are wounds of the liver or biliary passages. Such drains should not be brought out through the exploratory incision, where they will invite wound infection with possible evisceration, but should emerge through a separate short incision placed some distance from it. The unfortunate designation of such drainage wounds as "stab wounds" often leads the inexperienced to bring out drains through an aperture so small that the drain serves as a plug rather than a conduit. Free drainage requires an opening through skin, fascia, muscle and peritoneum of a size to admit two fingers. Otherwise the constriction of tissues about the drain frequently defeats its purpose.

Perforations of the small intestine are frequently multiple, and ordinarily occur in an even number. Since small intestine is never exteriorized, every perforation must be found and closed securely. Furthermore, the intestinal tract must be left with good blood supply and with an adequate, unobstructed lumen. When there are numerous wounds in a single segment, resection of the segment with end-to-end anastomosis may be the quickest and safest method of repair.

Because of the thinner wall and poorer healing properties, wounds of the colon must be handled differently than wounds of the small intestine. Intraperitoneal closure is avoided whenever possible, the injured colon segment being mobilized so as to permit its exteriorization without tension, the traumatic openings then serving to decompress the bowel externally as a colostomy. Wounds of fixed colon segments which cannot be exteriorized (the rectum and distal sigmoid) are closed primarily, and a proximal diverting colostomy is performed to protect the suture lines of the primary closure. The introduction of an intestinal antibiotic such as neomycin into the bowel lumen proximal to the repair affords added protection.

An injured loop which is exteriorized, or a proximal loop which is brought out for colostomy, must be brought out through an incision separate from the long exploratory incision, as is also the rule with drains. Wounds involving the rectum below the peritoneal reflection require proximal diverting colostomy along with drainage of the retrorectal space from below through a presacral approach[19]. In injuries of the bladder neck or the urethra the repair is protected by suprapubic cystostomy.

The debridement of the missile wounds is usually deferred until secure closure of the exploratory incision has been effected. Antibiotic therapy, usually with penicillin and streptomycin, is continued after operation, and gastroduodenal suction is employed until flatus is passed freely. Fluids, electrolytes and vitamins are administered parenterally and additional blood is given as indicated. Attention is directed toward the prevention of atalectasis, phlebothrombosis and other extraabdominal complications, postoperative care being continued as with other abdominal operations.

Summary

The high mortality from penetrating wounds of the abdomen was not altered significantly by surgery until means were developed to counteract massive hemorrhage and to control posttraumatic peritonitis. This is illustrated readily in reviewing the history of exploratory laparotomy as it has effected the survival of military and civilian victims.

Since World War I the progressively increasing use of blood transfusion, the development of dried plasma as an emergency blood substitute, and the

advent of the blood bank have made it possible to bring to surgery an increasing proportion of those critically wounded by abdominal penetrations and to sustain them through long and hazardous operations. During the same period the course of posttraumatic peritonitis has been influenced in a revolutionary manner through a succession of advances relating to such problems as prevention of distention and maintenance of fluid balance, and culminating in the discovery of antibacterial agents which are effective in the control of very many cases of sepsis. As a result, the individual who is shot or stabbed in the abdomen today, but who is not killed outright, has a considerably better chance to recover than he would have had at the close of World War II, and enjoys at least six times the prospect for survival that he would have had in the era of World War I. The progress of 40 years now bring three times as many of these wounded to surgery where the risk of the laparotomy performed has been reduced to at least one-third.

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Discussion

Dr. O. H. Wangensteen:—Dr. Moore's discourse has been most interesting and instructive. The real difficulty in instances of blunt abdominal trauma is to know when to operate. I can recall 20 years ago having watched a patient for some hours, who had just fallen backward while raking leaves in her yard. The abdomen was not opened and explored as early as it should have been. At operation, as a consequence of merely falling on her back, a large tear in the gut was found.

Perhaps no phase of abdominal surgery is more interesting than the history of operation for bullet wounds from small firearms. In 1901 when George Makins returned from the Boer War, he wrote a monograph on War Wounds, in which he outlined the expectant treatment of bullet wounds of the abdomen. In fact, the few recoveries observed followed conservative treatment. And so too, Nicholas Senn in reporting his experiences with gunshot wounds of the abdomen at the siege of Santiago in the Spanish-American War, indicated that conservative treatment was the best. When, however, in September, 1901, President William McKinley was shot at close range by an assassin with a revolver, the surgeon, Matthew Mann, a gynecologist by interest, elected nevertheless, and be it said to his great credit, to open the abdomen. A bullet wound penetrating both walls of the stomach was found, which Mann closed. The patient died approximately six days later. McKinley was a large man and Gaylord, who did the autopsy, spent seven hours looking for the bullet but failed to find it. The immediate cause of death was pancreatic necrosis, which outcome might in a similar instance have happened today too.

When World War I broke out, participants on both sides of the conflict were committed to conservative treatment of bullet wounds of the abdomen, in line with the admonition of George Makins of several years before. In fact, it was not until the war was well along when Enderlen and Sauerbruch showed in a control study that whereas the mortality was large, whether the treatment was operative or conservative, the results were nevertheless definitely better attending operative treatment. It seems strange indeed to us now, as we look back, that the conservative management of bullet wounds of the abdomen should have prevailed well into the second decade of this century.

Dr. Moore's paper deserves to be widely read. It details a fascinating story.

Dr. I. Snapper:—This really is a subject far removed from my actual interests. My recollections go back to the Boer War in the beginning of the 20th

Century. Then, due to the primitive circumstances under which they had to work the surgeons came to the conclusion that a soldier with a penetrating abdominal wound had a better chance to survive if he were left in peace than if he were operated upon. It was therefore interesting to hear that the modern experiences with such penetrating wounds of the abdomen are so much more favorable, thanks to our knowledge of pre- and postoperative care, antibiotics and wonder drugs.

There is an excellent, though old, method for diagnosis of intraabdominal hemorrhage. In the abdomen hemoglobin is transformed to hematin which appears in the blood where it is nowadays known as methalbumin. The presence of hematin in the blood can easily be demonstrated spectroscopically. If to the serum of such a patient a few drops of ammonium sufide or of hydrazin hydrate are added, then in the presence of hematin, hemochromogen is formed, characterized by a band located between the green and the yellow part of the spectrum. This band can be recognized in very dilute concentrations.

If in a patient with penetrating wound of the abdomen, hematin appears in the serum, considerable intraabdominal hemorrhage must have taken place.

Dr. Robert M. Moore:—I appreciate Dr. Snapper's interesting discussion. I was not acquainted with the hematin test, which appears to be very useful.

Dr. Snapper's remarks about the Boer War were most interesting. The British, at the outbreak of the War, advised medical officers to perform laparotomy in cases in which there seemed to be internal injury. After six months, however, they stopped the practice when they found that the mortality rate was lower when these patients weren't operated upon. Some thought this finding was the result of the small caliber rifles used by the Boers, the mucosa serving to plug the openings made by the small bullets. I think a better analysis was that made by Wallace, who, after reviewing the history of the Boer War from the standpoint of the Royal Army Medical Corps, related that distances were so great in the Boer War, and evacuation so interrupted, that by the time the wounded soldier reached a facility where surgery could be performed the issue usually was already settled. It was the wrong time for laparotomy.

I should disagree that penicillin has been the greatest element leading to the improvement in the mortality rate from gunshot wounds. I think most surgeons who deal with gunshot wounds of the abdomen would rather do without penicillin and other antibiotics than to have to do without a facility for blood transfusion. At least to me the blood bank rates first. It is interesting that in 1917, during the closing months of World War I, Richardson of the British Army established a bank of blood preserved with dextrose for use at Clearing Stations to transfuse wounded soldiers. Apparently it came too late in the war to receive much attention, and almost 20 years elapsed before the first blood

bank in the United States was established at the Cook County Hospital in Chicago, 19 years after Richardson's demonstration.

As to the closed or "non-open" wounds of the abdomen, they also present many problems. We have seen great injuries from wounds which seem to be of little severity, and many freakish occurrences. I see no practical method of management other than to consider each case individually, operating if and when there are signs of hemorrhage or evidences of peritoneal irritation.

Dr. Wangensteen:—Just for the record, I would like to say one thing. In this country, no penicillin was available to civilian practitioners of medicine until June, 1944, and then only in small lots to those professing a special interest in its use for certain diseases. A most dramatic fall in the mortality of appendicitis in this country occurred over the period beginning in 1940, long before penicillin was available. I would like to believe that our growth of knowledge relating to the cause of appendicitis, namely, obstruction, had something to do with that decrease in mortality.

GASTRIC HEMORRHAGE AS A COMPLICATION OF FLAIL CHEST*

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and

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With the known association of chronic pulmonary insufficiency and peptic ulceration and with our clinical impression that there was a similar relationship in acute insufficiency, we were prompted to review our cases of "flail chest", a condition due to trauma in which there are multiple rib fractures, paradoxical respiratory movements and usually marked respiratory embarrassment.

Review of Cases

During the five-year period from 1952-1956, 18 cases of flail chest were admitted to the University Hospital. Seventeen patients were injured in automobile accidents, the 18th in an industrial accident. All sustained moderate to marked respiratory insufficiency as evidenced by dyspnea, cyanosis and tachypnea. All presented paradoxical respiratory movements necessitating some form of external fixation, usually Kirschner wires through the presternal fascia to permit traction. Tracheostomy was performed in approximately 50 per cent of the patients and was a routine procedure on the indigent service to aid in bronchopulmonary toilet and to lessen the difficulty in removing the bronchial secretions associated with parenchymal injury of the lung[1,2]. Multiple injuries were present in 16 cases. The most frequently complicating injuries were hemopneumothorax (16), abdominal visceral injury (2), head injury (3), and extremity fractures (8). Two patients manifested ECG changes interpreted as evidence of cardiac trauma; one of these died with ventricular fibrillation. Peripheral vascular failure, when present, was treated with blood, electrolyte solution or dextrose in water as indicated. All patients evidenced severe stress reactions.

Of the five deaths in this series of 18 patients, three were associated with massive gastrointestinal bleeding. These occurred early in the series and prompted routine adoption of an ulcer regimen as part of the total program for patients with flail chest. This has seemed to be useful for there has been no known gastrointestinal hemorrhage in the cases so treated. The patients' records are abstracted below to identify the pattern of gastrointestinal bleeding:

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Department of Surgery, Medical College of Alabama.

Case 1:—E.H.R., a 48-year old white male fireman was admitted to the University Hospital approximately two hours after an automobile accident in which he sustained a chest and leg injury. He was not unconscious. There was no history of duodenal ulceration.

Examination revealed an obese male who was moderately cyanotic and in acute respiratory distress. Blood pressure was 90/60, pulse rate was 90. There was marked paradoxical movement to the anterior chest wall and sternum with decreased breath sounds over the left chest. Heart sounds were distant with an occasional extrasystole. The abdomen was negative. There was a compound left tibial fracture.

Admission laboratory studies revealed a Hgb. of 12 gm.; WBC of 21,300 and normal urinalysis. On the fourth hospital day the CO_2 combining power was 31.4 mEq./l. and gradually rose to 50.9 mEq./l. the day before death (the 17th hospital day). Bleeding, clotting, prothrombin times were normal.

Admission chest film revealed atelectasis of the left lower lobe without evidence of hemopneumothorax. The patient was placed in sternal traction and a tracheostomy was performed. He remained alert and cooperative. On the 12th postinjury day he passed a tarry stool with only a moderate increase in pulse rate. He continued to pass tarry stools and on the 17th day in the hospital he vomited copious amounts of blood. He received 3,000 c.c. of blood and in spite of all treatment, expired on the 18th hospital day. Autopsy was not obtained.

Case 2:—L.E.S., a 62-year old white female was admitted to the University Hospital approximately three hours after an automobile accident. She sustained multiple rib and extremity fractures. She was not unconscious. She had been previously admitted for a duodenal ulcer.

Examination revealed an obese female in obvious distress with dyspnea and moderate cyanosis. She was alert and cooperative. Blood pressure was 140/100; pulse rate 110. There was a flail chest with decreased breath sounds bilaterally. The heart and abdomen were negative. There were bilateral closed forearm fractures.

Urinalysis was negative; hemoglobin 12.5 gm.; WBC 17,900. On the sixth hospital day the CO_2 combining power was 29.3 mEq./l. and gradually rose to 34.3 on the tenth hospital day. No other hematological studies were done.

Initial chest film revealed bilateral hemopneumothorax. Sternal traction, tracheostomy and bilateral closed thoracentesis were done. Initially she did well, however, on the third hospital day she became somewhat stuporous and non-responsive. This continued and on the seventh hospital day she passed a tarry stool. She continued to have tarry stools and, on one occasion, hematemesis. She received 1,000 c.c. of blood. Her hemoglobin did not fall below 10 gm. On her 12th hospital day she expired without massive hemorrhage or shock. Probable

cause of death was posttraumatic pneumonitis with atelectasis and gastrointestinal hemorrhage. No autopsy was obtained.

Case 3:—E.M.O., a 65-year old civil engineer was admitted to the University Hospital shortly after an automobile accident. He was not unconscious. There was no previous history of duodenal ulcer.

Examination on admission revealed a hemopneumothorax on the right with multiple rib fractures and paradoxical respiratory movements. BP was not obtainable on admission.

Admission laboratory studies revealed a PCV of 46; WBC of 30,900 and normal urinalysis. CO_2 combining power on the sixth hospital day was 34.3 mEq./l.

Chest film revealed multiple rib fractures on the right, subcutaneous emphysema and pneumothorax on the right. Sternal traction and tracheostomy were performed while he was receiving 1,000 c.c. of blood, and the BP rose to approximately 100/60 and remained there. He responded well to initial treatment until the fifth hospital day when he began vomiting copious amounts of blood and having bloody diarrhea. He expired on the seventh hospital day in shock after having received a rapid transfusion of 1,000 c.c. of blood. No autopsy was obtained.

As a control group a series of automobile accidents of a similar degree of stress were reviewed. This series included 14 patients admitted to the University Hospital from 1952 to 1956 shortly after automobile accidents in which the major injury was a ruptured spleen. All underwent splenectomy. Nine of these patients had associated fractured ribs over the splenic area but none had evidence of paradoxical respiratory movements or respiratory insufficiency. Gastrointestinal bleeding was not observed in this group.

Comment

Acute upper gastrointestinal hemorrhage appears to be an especial hazard of flail chest injuries in this series. This was sufficiently severe to produce hematemesis in three patients on the fifth, seventh and twelfth days after injury. All three patients died and the acute blood loss was the major cause of death in two of these and a contributing factor in the death of the third patient. Only one of these patients had a prior history of peptic ulceration. Institution of a routine antacid program for patients with flail chests has been coincident with the disappearance of gastrointestinal bleeding as a complication of the injury. Gastrointestinal hemorrhage as a complication of flail chest has not been reported previously[3-6].

It is obviously important to determine whether or not gastrointestinal hemorrhage is a sufficiently frequent complication of flail chest to warrant the co

tinued adoption of routine antacid programs in prophylaxis of this complication. Two features of the injury, stress and CO_2 retention, have a known relationship to gastric hypersecretion and increased acid-peptic activity.

The role of stress in gastric erosion and peptic ulceration has been well documented but the mechanism remains obscure[7-12]. Drye and Schoen have demonstrated gastric hypersecretion in man 12 to 24 hours after major trauma, but the stimulus has not been defined[13]. Gray reported gastric hypersecretion in patients receiving steroid drugs[14], but these observations have not been generally confirmed[13,15,16]. The current viewpoint is that steroid therapy leads to peptic ulcerations through inhibition of mucosal healing of spontaneously occurring superficial erosions[13,17]. It is possible that these patients, with sudden increase of thoracic pressure at the time of injury, suffer secondary vascular pressure changes in the portal circuit with submucosal hemorrhages and subsequent mucosal erosion. Comparison of the clinical course of 14 patients with rupture of the spleen in consequence of similar direct violence does not support the concept that the combination of stress and compression is responsible for the observed bleeding from the gastrointestinal tract.

A common denominator in the morbid process producing fatal hemorrhage in the three patients presented here was marked pulmonary insufficiency with CO_2 retention. The CO_2 combining power ranged from 34.3 mEq./l. to 50.9 mEq./l. Several observers have noted a 20 per cent incidence of peptic ulceration in patients with chronic respiratory insufficiency[18-22]. Apparently, acidosis *per se* has little influence upon gastric acid secretion whereas CO_2 content of the blood has a significant effect[24]. Gastric hypersecretion with acid excess has been noted with experimentally induced CO_2 retention in normal adults by Apperly[23] and others[25,26]. It seems possible that CO^2 retention in the patients with a flail chest warrants further evaluation as regards the bleeding complication noted.

Although our most recent patients have received ulcer therapy on an expedient basis, it seems likely that a more direct approach should be utilized. Mörch[5,29] has developed a method of closed intermittent positive pressure insufflation to obviate external traction and to maintain respiratory alkalosis. Further studies of the patient with flail chest should correlate gastric secretion, blood p CO_2 and serum pH in an effort to answer the problems raised in this discussion. It would be helpful if others identified the incidence of gastrointestinal bleeding in similar patients with pulmonary insufficiency as a result of thoracic injury.

Conclusions

1. Peptic ulceration is a frequent complication of acute and chronic respiratory insufficiency.

2. Prophylactic ulcer therapy is useful in the over all treatment of acute respiratory insufficiency due to trauma.

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Discussion

Dr. I. Snapper:—The occurrence of gastrointestinal hemorrhage after laparotomies—even after appendectomies—was always explained by surgical stress. This concept was later developed by Dr. Cushing who implanted drugs into the brain of animals and observed the development of gastric ulcers.

It is important to know also that the stress caused by a flail chest is the cause of gastric hemorrhages.

Dr. O. H. Wangensteen:—Dr. Salter's paper has been interesting. I have seen flail chests, some of which were the results of overenthusiastic and extensive rib resections for tuberculosis. I do not now recall having seen the entity which Dr. Salter described today. I assume it is a form of stress ulcer; just how stress potentiates the occurrence of peptic ulcer of hemorrhagic gastritis is still obscure. Peptic ulcer is known to occur following severe trauma, including burns (Curling's ulcer) and following operations. German surgeons of the last generation, Eiselberg, Payr, and others, were inclined to credit the occurrence of gastric hemorrhage following abdominal operations to infarction of the omentum. Certainly, complications such as peritoneal infection, following operation, predispose to these occurrences.

During these sessions I have mentioned a method of dealing with massive gastric hemorrhage by conservative means. I refer to the use of local gastric hypothermia. Most of you are familiar with our employment of the esophagus of the intact cat in evaluating the potential digestive power of gastric juice.

The gastric juice from patients with duodenal ulcer when perfused through the cat's esophagus at body temperature for a period of two hours, at an outflow pressure of 20 cm. of gastric juice, results in perforation of the cat's esophagus in the majority of instances. The gastric juice obtained from the patients with duodenal ulcer has the greatest potential digestive power of any gastric juice my colleagues and I have examined. It was found when cats were exposed to systemic hypothermia (lowering of the body temperature to approximately 25° C., with the perfused gastric juice similarly cooled), that gastric juice obtained from patients with duodenal ulcer, which had perforated the warm cat's esophagus in two hours, failed to affect the esophagus of cool cats.

In a previous discussion [*Am. J. Gastroenterol.* 32: (Aug.), 1959] I referred to our work with frogs.

My colleagues, Drs. Peter A. Salmon, Ward O. Griffen, Jr., and Harlan D. Root, have made interesting studies on the relationship of temperature to gastric digestion in various species of animals. It was found, that save for the fish (trout and cat fish), all the usual laboratory animals, including rats, rabbits, cats and

dogs have a suspended digestion at lower temperatures. And so similarly with man too, as bolus studies of meat placed in man's stomach have demonstrated, when the stomach is kept cool. Also *in vitro* studies suggest very definitely that the peptic digestive power of the juice was almost completely inhibited at temperatures below 10° C. Moreover, no injury to the esophageal wall of the cat occurred over a two-hour period of infusion when N/10 HCl was dripped through it.

In addition to the observed depression of peptic activity, there occurs also, in consequence of cooling, considerable depression of the amount of gastric secretion. Similarly, blood flow studies have shown that the arterial inflow to the gastric wall is considerably diminished.

A preliminary paper has already appeared in the August 1958 issue of *Surgery* (44:265) on these observations. An increased experience since then indicates that, local gastric cooling is a fairly effective means of dealing with the problem of esophageal varices too. It is not the intraluminal pressure—but the interruption of peptic activity and reduction of arterial inflow which account for the effectiveness of the method in dealing with the bleeding of varices. It would appear that the method may well have real virtue in the management of patients with massive gastric hemorrhage, especially from the peptic-ulcer diathesis. In conditions, in which there is a hemorrhagic dyscrasia of one sort or another, it is not to be expected that, local gastric cooling would be very effective. During the cooling, the patient is warmed peripherally so that his rectal temperature stays at the normal level.

In casting about for other areas in which local gastric cooling could be used effectively, we have cooled the heart by perfusing ice cold saline solution through the pericardial sac. Cold blood also has been transfused through the coronary arteries by cross-clamping the aorta, employing a pump oxygenator and inflow stasis; prompt slowing of the heart beat and cardiac arrest can readily be produced in this manner.

Another area in which local cooling has been employed effectively is in thwarting the secretion and rise of intraluminal pressure within the obstructed rabbit's appendix. As Dr. Clarence Dennis, my erstwhile colleague now of New York, and I showed (*Ann. Surg.* 110:629-647, 1939), following ligature of the base of the rabbit's appendix, perforation will occur in approximately two-thirds of the instances after ten hours. On the contrary, when the rabbit is cooled, either systemically or locally, perforation of the appendix does not occur. Similarly the rise of pressure which approximates systolic blood pressure in the warm rabbit—these pressures fail to develop in the lumen of the rabbit's appendix when cooled. So similarly, too, with obstructed closed loops of duodenum in the rabbit. In the cooled animal, there is a marked reduction in secretion and the rise of intraluminal pressure is slight.

Another occurrence which rather surprised us is the cessation of motility of the intestine attending cooling. We had anticipated that the motility might be enhanced under these conditions. This cessation of motility of the gut and diminution of secretion suggests that mild systemic gastric cooling could be employed usefully in dealing with the intractable diarrheas that threaten life. Moreover, virtual cessation of intestinal motility accompanying cooling suggests that it might be possible to introduce cold solutions into the stomach to inhibit peptic activity and suppress gastric secretion and reduce arterial inflow without the use of the balloon. Under these conditions, obviously, there would have to be some mechanism developed to establish the continued circulation of cold fluid and to provide for its removal; otherwise, there would be regurgitation into the esophagus which would invite tracheal aspiration*.

How long gastric cooling should be continued is an interesting question. In patients with bona fide gastric or duodenal ulcer, as soon as the loss of blood has been controlled, usually after a period of five to eight hours' cooling, granted the vital signs have improved, and the hemoglobin has risen, and it is no longer necessary to continue transfusions to support a rising hematocrit, the balloon is withdrawn. A drip of cold milk, at a rate just fast enough to obviate ready emptying, is started immediately. This is done through a small polyethylene catheter, to which the patient usually registers no objection. Close watch is kept on the hemoglobin, the pulse, and other signs. If evidence of bleeding recurs, operation is undertaken. In patients bleeding from esophageal varices, following staunching of the bleeding, granted the patient is in good condition, we have come to feel that a definitive operation should be undertaken fairly directly, if the patient's general condition is good. In instances of intrahepatic block, a portacaval shunt can be done; in instances of extrahepatic block, excision of the entire acid-secreting area of the stomach is done with anastomosis of the esophagus to the antrum, or a Roux-Y type of restitution of esophagointestinal continuity may be preferred.

In the flail chest which Dr. Salter reported upon today, I believe one of the first things to do would be to secure adequate immobility of the chest, if possible. If ribs have been resected, these should be rewired. If the sternum has been fractured, fragments need to be stabilized securely. His report confirms the impression that a complicated convalescence from a major operative procedure potentiates the peptic ulcer diathesis.

Dr. Paul P. Salter, Jr.:—I should like to agree with Dr. Snapper. We feel that probably stress is the cause of ulceration in our patients. As I stated, since 1952 many papers have been published relating gastrointestinal ulceration to

*More recently, in the laboratory, my colleagues, Drs. Peter A. Salmon and Ward O. Griffen, Jr., have demonstrated that it is feasible to perfuse the stomach in this manner. It is necessary of course to employ solutions which have an osmotic equivalence of the electrolytes of the blood to preclude severe loss of electrolytes.

emphysema. They suggested the stress, CO_2 retention and emotional factors of emphysema as causes for the increased incidence of ulceration, particularly gastric ulceration. One paper studied one hundred-or-so patients with gastric ulcers, and found 43 per cent of them had emphysema. What this relationship is, we don't know.

It is of interest, as you all know, that you can reduce gastric acid secretion by giving Diamox. Diamox inhibits carbonic anhydrase and possibly decreases acid secretion by affecting the carbonic anhydrase of the gastric mucosa. Experimentally Diamox administration causes a persistent fall in blood CO_2 content during the period of administration. This may account for the decrease in gastric acid secretion.

I want to thank Dr. Snapper and Dr. Wangensteen for their remarks.

I have a patient with a duodenal ulcer who sent me a card which reads: "Ulcers are caused by not what you eat but what eats you." (Laughter)

CLINICAL EXPERIENCE WITH A NEW LONG-ACTING ANTACID-ANTICHOLINERGIC PREPARATION

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Preoccupation with laboratory and diagnostic procedures frequently leads one to overlook the importance of considering the patient in his total environment. Too often clinical studies are performed under conditions unlike those in which the physician usually sees his patients, thereby removing or adding factors which must exert an effect on the patients and their response to therapy. It is obvious that relief of symptoms must be a primary consideration in the treatment of peptic ulcer and other gastrointestinal disorders, and that this is an important criterion in determining the usefulness of any new therapeutic agent.

TABLE I

DIAGNOSIS

Duodenal ulcer		21
Gastric ulcer		1
Anastomotic ulcer		1
Gastroenteritis		18
Spastic colitis		7
Pylorospasm		15
Hypertrophic gastritis		4
Duodenitis		5
Duodenal diverticulum		2
Amebic colitis, cholelithiasis with diarrhea, diverticulosis coli, hiatus hernia	Each	1
		78

These thoughts prompted a clinical evaluation of a new anticholinergic-antacid preparation* in the framework of an office practice, where, after all, the majority of patients are examined and diagnosed and where treatment is prescribed and then appraised. Weiss et al[1] have recently reported excellent results with this preparation in a variety of gastrointestinal disorders, and to these we add the data derived from the study described here in the hope that they may contribute to an over all assessment of this preparation.

*BepHan Spacetabs.

Material and Method

The preparation used was BepHan Spacetabs, a tablet containing aluminum hydroxide glycine 450 mg., magnesium oxide 60 mg., and Bellafoline 0.5 mg. According to the manufacturer†, the magnesium oxide and Bellafoline are incorporated in an inert binding material from which they are released slowly in order to extend the duration of their therapeutic activity.

This preparation was employed in 78 patients over a period of 11 months. There were 36 females and 42 males in this series, their ages ranging from 12 to 75 years. Diagnoses (Table I) were made on the basis of history and thorough physical examination, two elements of the work-up which are extremely revealing and which, unfortunately, are too often relegated to the background, and were confirmed by gallbladder and gastrointestinal series as well as barium enema in all patients except those with acute gastroenteritis.

TABLE II

Effect of BepHan Spacetabs on Gastrointestinal Symptoms

Number of Patients	Symptoms**	Results*		
		Excellent	Good	Poor
36	Burning	27	9	—
37	Pain	27	8	2
20	Nausea	14	3	3
11	Eructations	10	—	1
9	Bloating	5	2	2
11	Vomiting	7	2	1
6	Diarrhea	4	1	1
4	Constipation	1	1	2
2	Bleeding	2	—	—

*Excellent—marked to complete relief of symptoms.
Good—moderate relief of symptoms.
Poor—no or inadequate relief.
**Some patients presented more than one symptom.

Because there was no previous experience concerning dosage, patients were started on doses ranging from two to four tablets daily. Chewing the tablets before ingestion was recommended to insure greater dispersion of the tablet contents. The schedule was altered to suit the patient's needs, depending on the degree of symptomatic relief and toleration.

An analysis of the case reports shows that the optimal dosage in 46 patients was one tablet twice daily (on arising and at bedtime). Twenty-three patients

found maximum comfort with one tablet three times daily (an added tablet at midafternoon). Six patients required one tablet four times daily, given before meals and at bedtime. Three patients obtained satisfactory relief with one-half tablet four times daily.

Results

Good to excellent results, signifying moderate to marked or complete relief of symptoms, were obtained in the majority of cases (see Table II). Epigastric burning (also described as heartburn or gnawing) was the most common symptom, and was usually relieved within 15 minutes. This was one of the most noteworthy features of the therapeutic effect demonstrated by this preparation. Equally satisfactory was the relief of generalized or localized abdominal cramping pains in the patients with spastic colitis. A concomitant reduction in the

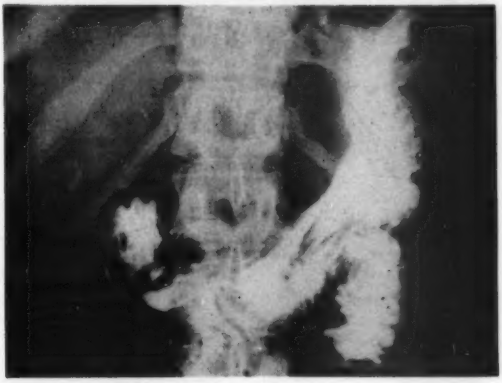

Fig. 1a—47-year old white female with typical peptic ulcer symptoms. 3 March 1958—shows a prepyloric ulcer.

incidence of nausea, vomiting, diarrhea, eructations and "feeling of abdominal pressure" was obtained. Bleeding in two patients with acutely active ulcers stopped within 24 and 36 hours after starting BepHan and frequent milk and cream feedings. One of these patients had bled for one week on previous therapy.

A markedly greater therapeutic effect was obtained when the tablets were chewed before swallowing. This confirms the experience of Weiss and his coworkers[1] and is now a routine recommendation in prescribing this preparation.

The prophylactic value of two to four of these tablets daily was amply demonstrated in many cases by the prevention of further gastrointestinal symp-

†Sandoz Pharmaceuticals, Hanover, N. J.

toms. Three patients who had experienced the customary spring-fall occurrence of duodenal ulcer the past two years have now gone through three "ulcer seasons" asymptomatically on a regimen of BepHan Spacetabs and modified diet.

The ulcers in all but one patient showed evidence of healing or were healed at the time of the second radiological examination, four to eight weeks after the initial series. Figure 1 illustrates a representative response to treatment. One patient's gastric ulcer required three months to heal, confirmed by x-ray. One year later, a severe emotional strain precipitated a recurrence which re-

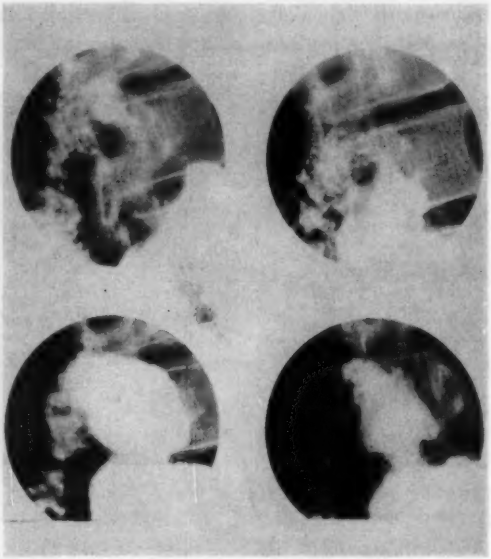

Fig. 1b—Same patient, 15 April 1958—shows complete healing of the ulcer after BepHan Spacetabs and diet.

quired hospitalization. Two weeks treatment with BepHan, supported by a strict diet was rewarded by a complete recovery (see Fig. 2). A female patient, age 51, had a marked hypertrophic gastritis strongly suggestive of polyposis. A regimen of BepHan and diet restriction, however, resulted in healing of the gastric mucosa, as evidenced by radiological examination (see Fig. 3).

Forty-seven patients provided data concerning onset of action. Of these, 43 noted relief of their symptoms within 15 minutes after swallowing a chewed tablet, while 4 patients said that this was evidenced within 30 minutes.

The effect of BepHan Spacetabs was most rapidly demonstrated in a group of 17 patients in whom the diagnosis of gastroenteritis was made. These patients exhibited upper gastrointestinal symptoms—nausea, vomiting, anorexia, heartburn, and/or a "sense of fullness", occasionally associated with episodes of diarrhea. These symptoms were of nonspecific etiology, brief in duration and not associated with any known organic gastrointestinal disease. Without exception, all of these patients were afforded marked relief within a few minutes

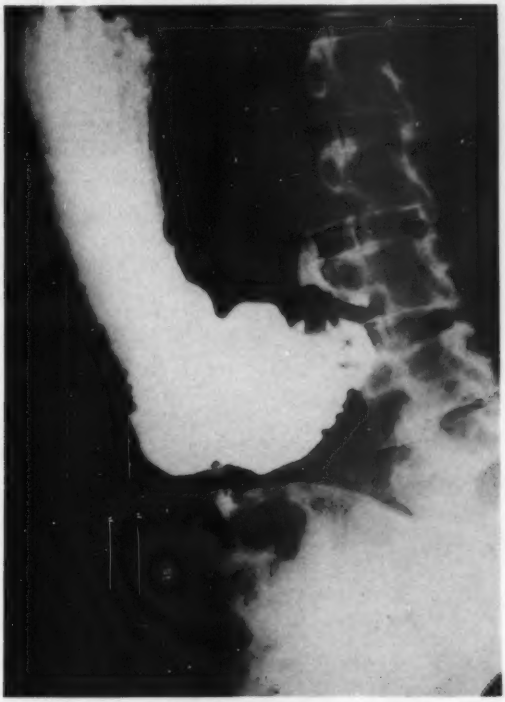

Fig. 2a—33-year old white female with a gastric ulcer 27 April 1957.

after ingestion of one BepHan Spacetab. The response was so rapid and so complete that all but one were able to eat at the time of their next meal.

A comparison of the effectiveness of BepHan Spacetabs with that of other agents previously employed was possible in 39 patients who had been under prior treatment with various regimens, consisting essentially of antacids and anticholinergics, taken separately. The patients were asked to indicate which preparation had been most helpful to them and to use their own words in describing the degree and nature of relief obtained. Granted that some patients

react well to any new preparation for a while, only those patients who had provided what were considered to be sound estimates of therapy previously employed were asked to make this comparison. Since office patients are generally more reliable and assiduous in returning for follow-up visits, a more valid appraisal of their response over a longer period of time is obtained.

Among the 39 patients, 30 rated BepHan Spacetabs more effective, 7 could distinguish no difference, and 2 stated that they preferred the previous treatment. One of the latter cited her inability to tolerate the peppermint flavor of

Fig. 2b Fig. 2d

Fig. 2b—Same patient 6 June 1957—ulcer healed with antacid and antispasmodic therapy.
Fig. 2d—Same patient, 23 June 1958—ulcer healed with BepHan and diet.

the BepHan Spacetab in the morning as her only reason for preferring the previously employed preparations. It is interesting to note that this was the only complaint concerning the taste of this preparation, for at the outset, it had been thought that the patients might object to the flavoring contained in these tablets. To the contrary, however, the comment was frequently made that this was preferable to the "chalky taste" of some other preparations.

A review of the case reports reveals some interesting notations concerning the comments of individual patients. One ulcer patient reported that he was now able to smoke a pack of cigarettes a day and to venture dietary indiscretions more frequently than before with absolutely no distress. Two business executives with ulcers stated that they were surprised that they were suffering much less discomfort despite intensified business pressures. The most frequent comment related to the relief obtained with two to four tablets daily and how much more preferable this was to previous regimens in which 6 to 14 tablets

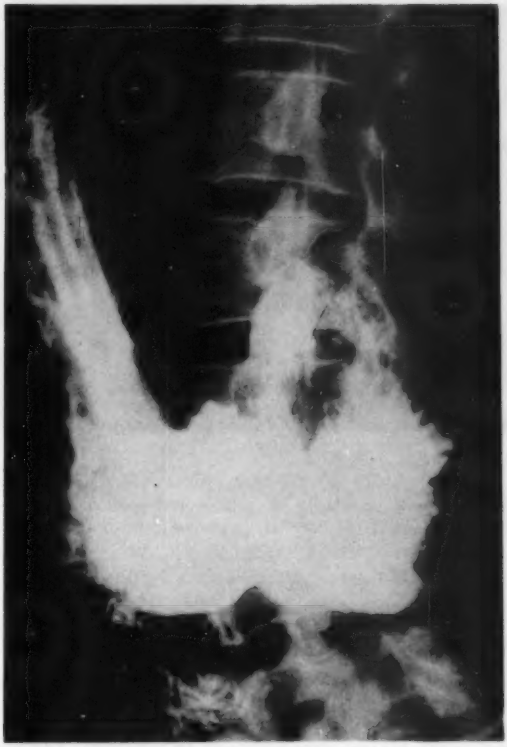

Fig. 2c—Same patient 2 June 1958—ulcer recurred while therapy discontinued.

were required daily. Improved sleep patterns were reported by several patients and these may possibly be attributed to more prolonged suppression of night pain.

Toleration

Dry mouth was reported by one patient on a dose of two tablets daily and by six patients taking three BepHan Spacetabs daily. The latter dose produced

blurring of vision in four patients. These complaints were voiced during the earlier stages of therapy and dissipated as treatment continued. Three patients obviated these by taking one-half rather than a whole Spacetab for each dose. There was no complicating change in bowel habits or any sign of alkalosis.

Comment

The difficulties involved in making valid estimates of antacid and anticholinergics have been well summarized by Kirsner[2]. He points out that an accurate appraisal of ulcer therapy is difficult, if not impossible, to achieve, especially when one considers that spontaneous fluctuations in gastric secretion are many and varied and that these must exert an influence too frequently overlooked in clinical evaluations.

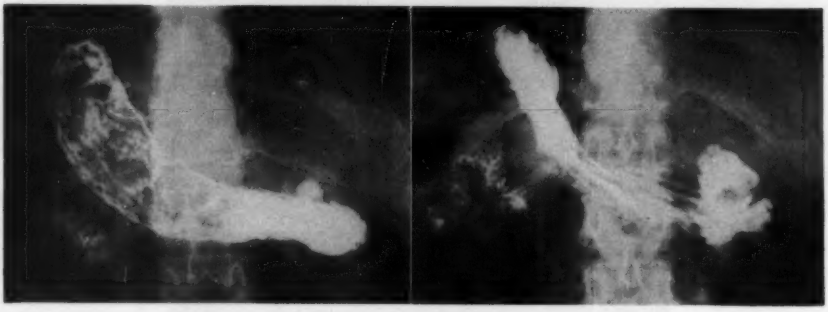

Fig. 3a Fig. 3b

Fig. 3a—51-year old white female. 27 February 1958—Cobblestone appearance of hypertrophic gastritis, with nodularity suggesting polyposis.
Fig. 3b—Same patient 14 April 1958—Healed gastric mucosa after BepHan and diet.

It seems fair to say that estimates of a drug's efficacy on the basis of symptomatic relief may well serve a useful purpose when one considers that even precise studies have their shortcomings. Granted that clinical evaluations based on subjective response do not tell us how much acid has been neutralized or to what extent hypermotility has been reduced, they often provide some very practical information that may be more valuable in terms of patient benefits than that derived from highly experimental procedures. Considering the fact that the gastrointestinal tract is extremely responsive to external stimuli, especially emotional influences, it would seem that the physician who is "close" to his patient is in a better position to elicit and weigh these in assessing the usefulness of a new drug than the investigator operating under more impersonal conditions. Emphasis on laboratory and x-ray studies too often blinds the investigator to the great value that derives from a careful history, and here, the ability of the physician to be a good "listener" probably outweighs any other consideration in the work-up of the patient.

Over and above the specific effect on symptoms, it is quite apparent that the simplified administration and reduced number of tablets of this regimen has contributed to the clinical benefit derived from this preparation. This observation has been made over a sufficiently long period of time to indicate that it must be related to the efficacy and prolonged activity of this preparation, since ulcer patients are notoriously prone to complain when their symptoms are not adequately controlled. The feeling of confidence in this program on the part of the patients cannot be overlooked as an important factor in the total (emotional and physical) management of such cases. The sense of well-being observed in these patients has also been noted by others[1].

Summary

A new preparation, BepHan Spacetabs, has been evaluated in 78 patients to determine its usefulness in the treatment of a variety of gastrointestinal disorders.

The results obtained in this series of cases indicates that this combination of an anticholinergic and two antacids was extremely effective in relieving the diverse symptoms exhibited by these patients. It was a helpful means of controlling and preventing symptoms of peptic ulcer, especially burning and pain, as well as for treating the acute symptoms of gastroenteritis.

Over and above its clinical efficacy, the practical value of this preparation was reflected in two other important advantages—the reduced number of tablets required to relieve symptoms and the simplicity of administration.

Conclusion

The medical management of peptic ulcer is essentially nonspecific and geared to symptomatic relief. The chronic nature of this disorder and the necessity for long-term treatment suggest that effective therapy should preferably be of extended duration, uncomplicated and not burdensome to the patient.

This study has demonstrated that BepHan Spacetabs fulfill these criteria to a high degree. Moreover, the results obtained in the treatment of gastroenteritis were so encouraging as to warrant further study of this preparation in such cases.

The over all response in this series of cases supports the conclusion that BepHan Spacetabs represent a highly useful agent in the management of gastrointestinal disorders.

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President's Message

In October 1960 the American College of Gastroenterology will hold its Twenty-fifth annual convention in Philadelphia.

The convention will mark 25 consecutive years of national meetings of an organization founded in 1932 by a small group of men with a common interest and an expressed purpose to maintain and promote the highest standards in medical education, medical practice and research in gastroenterology.

It is well to take stock of what has been accomplished. The practice of gastroenterology is firmly established today as a recognized subspecialty of internal medicine.

Our organization has contributed a journal which has improved over the years, regional meetings, annual conventions and annual postgraduate courses to disseminate the latest knowledge and progress in gastroenterology. These are useful functions and are expected of a medical organization such as ours.

There are some who feel that in recent years gastroenterology as a specialty has not made as rapid progress as one would ordinarily anticipate.

In looking for an explanation it would seem that the following must be noted. The greatest interest for most of us is clinical gastroenterology which is as it should be.

Yet we must not lose sight of the fact that progress in medicine depends on research.

Our organization, through its members, must take an active part in creating, directing and supporting gastrointestinal research projects. We must do everything in our power to direct available funds and new grants into gastroenterological research.

These research projects will in turn attract the young graduate and stimulate renewed interest in gastroenterology.

It is a great honor and a privilege to serve as president of the American College of Gastroenterology. I am grateful for the opportunity.

Jos. Shaiken

In Memoriam

We record with profound sorrow the passing of Dr. Anthony Bassler of New York, N. Y., Fellow and Honorary President and Dr. Samuel S. Feuerstein of Long Island City, N. Y., Fellow of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

Tributes to the late Dr. Bassler will be published in an early issue of THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

ABSTRACTS FOR GASTROENTEROLOGISTS

STOMACH

THE CARE OF PATIENTS AFTER GASTRECTOMY: Therapeutic Notes: Scottish M. J. 3:325 (July), 1958.

Care of patients after gastrectomy is very important. Following this type of surgery the acid secretion is reduced to normal, or below normal, so that alkalis and antacids are unnecessary. After operation the patient should be told that he is not an ulcer case any more, and must start a new "digestive life". The storage capacity of the patient's stomach is much smaller following this type of surgery and, therefore, size of meals should be limited. Patient must decide for himself how much he can eat at each meal and be comfortable.

All medication should be stopped. Patient should only take iron; this is to combat anemia, which is always present after gastrectomy.

Many different types of symptoms can appear. Some are mechanical factors which may require further surgery. Vitamin deficiencies due to malabsorption can also be present.

The "postcibal" syndrome is described and treatment is indicated. This syndrome is associated with epigastric distention and a feeling of heaviness. Simple measures are used in its treatment.

ABRAHAM BERNSTEIN

MANAGEMENT OF THE PATIENT WITH GASTRIC CANCER: George T. Pack. Northwest Med. 57:885 (July), 1958.

Cancer of the stomach seems to be decreasing in the United States while cancer of the lung, colon, and rectum have increased. About 15 per cent of cancer deaths are due to gastric cancer.

It is not difficult to diagnose established cancers of the stomach, but early cancer has many problems that the author discusses very well—size, location, and therapeutic healing. He states most ulcers on the greater curvature are malignant, and that most ulcers on the lesser curvature, near the incisura, are benign. The frequency of ulcerocancer and benign gastric ulcer at the cardia on the lesser curvature is 50-50. Ulcers in the immediate prepyloric area on the lesser curvature have been malignant in 65 per cent of cases.

The gastroscopic examination helps. Gastric analysis is not as helpful.

As to the surgical aspect of the problem he emphasizes that in cancers of the distal third of the stomach a subtotal gastrectomy is done removing the entire lesser curvature. A perigastric lymph node dissection is completed. The spleen and pancreas are not molested. Anastomosis is done, employing the greater curvature side of the fundus. The lymph nodes along the hepatoduodenal ligament and along the superior margin of the pancreas are dissected and removed.

In cancers of the middle segment of the stomach metastatic dissemination to so many groups of nodes occurs that he believes total gastrectomy should be employed. He also does splenectomy and subtotal distal pancreatectomy, removing the pancreas up to the level of the crossing of the superior mesenteric vein in association with the total gastrectomy.

In the case of cancers of the proximal third of the stomach, it has been found that remote metastases even into the infrapyloric group of glands occur in 14 per cent of the cases and to other groups with fairly high frequency. Therefore, for cancers of the gastric cardia, unless there is some contraindication, he does a total gastrectomy of the extended type with splenectomy and subtotal pancreatectomy. If the patient is elderly or a poor surgical risk and has a very early cancer an abdominal or transthoracic cardiectomy might be done.

The question of substitute stomachs was raised and various devices have been employed. A section of the transverse colon has been used between the esophagus and duodenum, and a segment of the jejunum is now enjoying some popularity. The right half of the colon has been interposed between the esophagus and the duodenum. These transplants may act as reservoirs. Fat absorption is just as bad in these patients as it is in total gastrectomy without a reservoir. The way to combat the syndrome is to give patients a high protein, high fat diet with minimal amount of carbohydrates.

The author gives a definitive cure rate, comparing his experiences of the period from 1931 to 1955. About 50 per cent are noncurative operations. The duration of symptoms has no influence on the operability of gastric cancers. Age seems to make very little difference except in patients under 40. In the younger group, opportunities are less favorable for carrying out curative operations. It remains about the same until around 80 years. Operative mortality goes up at a rapid rate with advancing age and becomes almost prohibitive in patients over 70. There is a relationship between the number of 5-year survivals and the type of symptomatology. Patients with ulcer syndrome are the most favorable. Second is the group who had cryptic anemia leading to early discovery of cancer. Patients whose predominant symptom was indigestion had a very low cure rate, less than 7 per cent because perhaps this discomfort was readily tolerated and self-treated. Polypoid and ulcerating cancers offer the best prognosis with 44.8 and 45.5 per cent survivals. Cancers with ulceration and infiltration had only 20 per cent cures and cancers of the diffusely infiltrating type were cured in only 6 per cent of the cases.

Survival figures show most recurrences are found within the first 3 years after gastrectomy regardless of whether nodes were involved or whether cancer was diffusely infiltrating or not. A patient living 3 years beyond gastrectomy for cancer will probably live out his life expectancy unless he dies with an intercurrent disease.

Gastric cancer is still a most serious problem, and the number of patients salvaged by these operations is not great enough to cause rejoicing.

I. Henry Einsel

INTESTINES

LEIOMYOSARCOMA OF THE ASCENDING COLON ASSOCIATED WITH MULTIPLE POLYPOSIS. Donald F. Guisto, Morton J. Thoshinsky and Louis G. Brizzolara. Am. J. Surg. 95:1007 (June), 1958.

The writers feel that this is the first reported case of leiomyosarcoma of the large bowel, associated with multiple polyposis. Leiomyosarcoma of the large bowel, exclusive of the rectum is a rare condition. The literature reveals only 14 reported cases, and their report is the 15th case of leiomyosarcoma of the large bowel, and the first

case associated with multiple polyposis.

A case report reveals that a 27-year old white male was admitted to a Veterans Administration hospital with the complaint of diarrhea of four months' duration. The physical examination was essentially negative except for a healed right McBurney scar overlying a freely movable, slightly tender, mass in the right lower quadrant. On sigmoidoscopic examination, many small sessile polyps, ranging in size from 2 mm. to 4 mm. in diameter, were found. Barium enema revealed three large polypoid masses: the largest being in the area of the ascending colon; and two smaller masses, one was in the splenic flexure and one in the sigmoid colon.

At operation, the findings by x-ray were confirmed. There was no evidence of metastases to the liver or to regional lymph nodes. Subtotal colectomy was performed.

The smaller tumors and sessile type of polyps showed no evidence of malignancy and were benign adenomatous polyps. Twenty-four lymph nodes removed from the specimen showed no evidence of metastases. The patient made a good recovery.

On follow-up treatment, several small polyps were biopsied on protoscopic examination, and fulgurated. Because of cellular atypism of the polyps, excision of the remaining rectum was contemplated.

CARL J. DEPRIZIO

CARCINOMA OF THE DUODENUM: REVIEW OF THE LITERATURE FROM 1948 TO 1956: H. L. P. Resnik and Donald R. Cooper. Am. J. Surg. 95:946 (June), 1958.

Primary carcinoma of the duodenum is a rare condition, and an almost uniformly fatal disease. The poor results are due to two major factors: first, the difficulty in making an early diagnosis by clinicians and roentgenologists, and secondly the reticence of surgeons to attack the lesions as aggressively as other gastrointestinal carcinoma.

To eliminate confusion, the writers of this paper speak only of supra- and infrapapillary lesions of the duodenum. Duodenal lesions are distributed equally above and below the ampulla of Vater. There is no predisposition to race or sex, and they occur most commonly in the 5th and 6th decades of life.

Ulcer-like pain, nausea and vomiting are common symptoms in both types of lesions, but gastrointestinal hemorrhage is seen in almost 50 per cent of the infrapapillary cases. The writers include nine cases, four had suprapapillary and five had infrapapillary carcinoma. Vomiting was a presenting symptom in eight of the nine cases, and melena and anemia was found in all of the infrapapillary lesions.

The ulcer-like syndrome does not respond to ulcer regimen.

Differentiation by symptoms of lesions of the suprapapillary, peripapillary and infrapapillary regions is most difficult and one would do well merely to suspect the lesion and suggest immediately x-ray examination. In eight of the nine cases, x-ray pointed to the diagnosis. X-ray statistics reveal that this lesion appears about once in every 5,000 gastrointestinal series.

The treatment is drastic radical pancreaticoduodenectomy at the earliest possible stage.

CARL J. DEPRIZIO

MANIFESTATIONS OF SMALL BOWEL TUMORS: Mack F. Bowyer. Texas J. Med. 54:480 (July), 1958.

Small bowel tumors are not rare, though uncommon, and most are malignant. The preoperative diagnosis is only made in about 10 per cent of cases, therefore awareness by the clinician and radiologist is advocated when gastrointestinal bleeding or anemia is associated with recurrent abdominal discomfort, and investigation fails to reveal the commoner causative lesions.

This series of 10 cases represents 3 adenocarcinomas, 1 sarcoma, 2 carcinoids, 3 polyps, and 1 hemangioma. The Peutz-Jeghers syndrome was encountered once, in a seven-year old boy with typical melanin spots on the face, lips, mouth, and hands, and who has had 10 polyps removed from his small bowel. Both carcinoid cases revealed metastases, and removal of the primary mass was followed by good health for 2 years and 5 years, thus far, proving the desirability of this procedure. Mallory reported one case 20 years postoperative,

where the metastases were quiescent, after excision of the primary tumor. The biologic assay for serotonin derivatives is mentioned in a brief description of the carcinoid syndrome.

NORMAN L. FREUND

LIVER AND BILIARY TRACT

FATTY LIVER IN CHILDREN—KWASHIORKOR: Silvestre Frenk, Federico Gomez, Rafael Ramos-Galvan and Joaquin Cravioto. Am. J. Clin. Nutrition. 6:298 (May-June), 1958.

Liver steatosis may occur with primary malnutrition (Kwashiorkor) or secondarily with any wasting disease. Regardless of the amount of fat in the liver cells there is always a marked decrease of the cytoplasm. At the same time there is an increase of water and glycogen in these cells. Liver function tests vary in their results. Serum bilirubin and cephalin flocculation are usually normal. BSP retention and serum protein pattern are abnormal. Hypoalbuminemia is caused by insufficient protein intake which is also responsible for hypoaminoacidemia and for low values of protein enzymes for instance, cholinesterase and alkaline phosphatase. An impairment of phenylalanine conversion is responsible for the change of hair color to red. Abnormal carbohydrate metabolism is shown by attacks of hypoglycemia as well as by hunger diabetes. Serum cholesterol is decreased, especially cholesterol esters. Total lipids are decreased especially alphalipoproteins. Best treatment for nutritional liver disease is a well balanced diet. The influence of lipotropic agents is questionable.

H. B. EISENSTADT

GALLSTONE ILEUS: Thomas J. Foley and Jack Selzer. Wisconsin M. J. 57:253 (July), 1958.

Seven cases of gallstone ileus are presented by the authors. Although it is difficult to make a definite diagnosis of gallstone ileus, it should be suspected in patients who give a history of previous gallbladder disease, symptoms of acute small bowel obstruction, abnormal communication between the biliary passages and the intestinal tract as seen by air or other contrast media, direct or indirect visualization of stones in the intestinal tract, and x-ray evidence of complete or partial intestinal obstruction.

Treatment must be individualized but all must be immediately prepared for exploratory laparotomy. The stone if possible should be removed through an enterostomy in apparently normal bowel adjacent to the gallstone. Because of the high rate of recurrence of gallstone ileus, cholecystectomy is mandatory when other large stones are present in the gallbladder sac. No attempt should be made to repair the cholecystoenteric fistula.

A. J. BRENNER

PROGNOSTIC SIGNIFICANCE OF THE GALACTOSE TOLERANCE TEST IN THE RHYTHM OF THE LIVER: R. Boller and H. Partilla. Am. J. Digest. Dis. 3:492-501 (July), 1958.

One hundred seventy-five cases of liver or biliary tract diseases in which the galactose tolerance test was performed during the night and during the day are discussed. The authors found differences in the results of night versus day tolerance tests which they relate to the "rhythm of the liver". In cases of severe hepatitis the night galactose tolerance test is often positive right from the beginning while the day test becomes positive later. The night galactose tolerance test usually becomes lower than the day test after 3-4 weeks of treatment. A constantly high night galactose tolerance test is a sign of serious prognosis.

WALTER CANE

PSYCHOSOMATIC MEDICINE

TRANSVESTISM AND PRURITUS PERINEI: Nahman H. Greenberg and Alan K. Rosenwald. Psychosom. Med. 20:145 (Mar.-Apr.), 1958.

Intractable pruritus may be entirely due to psychiatric causes. Pruritus has been explained as the condition of combined pleasure and pain with aggressive elements leading to self-destruction. It is also a masturbatory equivalent and may be associated with homosexuality. The case of a male patient is described where intractable anal and perineal pruritus was associated with transvestism, the "acting-out" of the fantasy of being a woman. The transvestism was apparent since childhood. However, the itching started during the first pregnancy of the patient's wife. He participated in all the symptoms of her pregnancy such as nausea and vomiting, but had intractable itching at the same time. No treatment improved his condition except the changing into female clothes. He finally wore women's clothes continuously and was cured by an emasculation operation.

H. B. EISENSTADT

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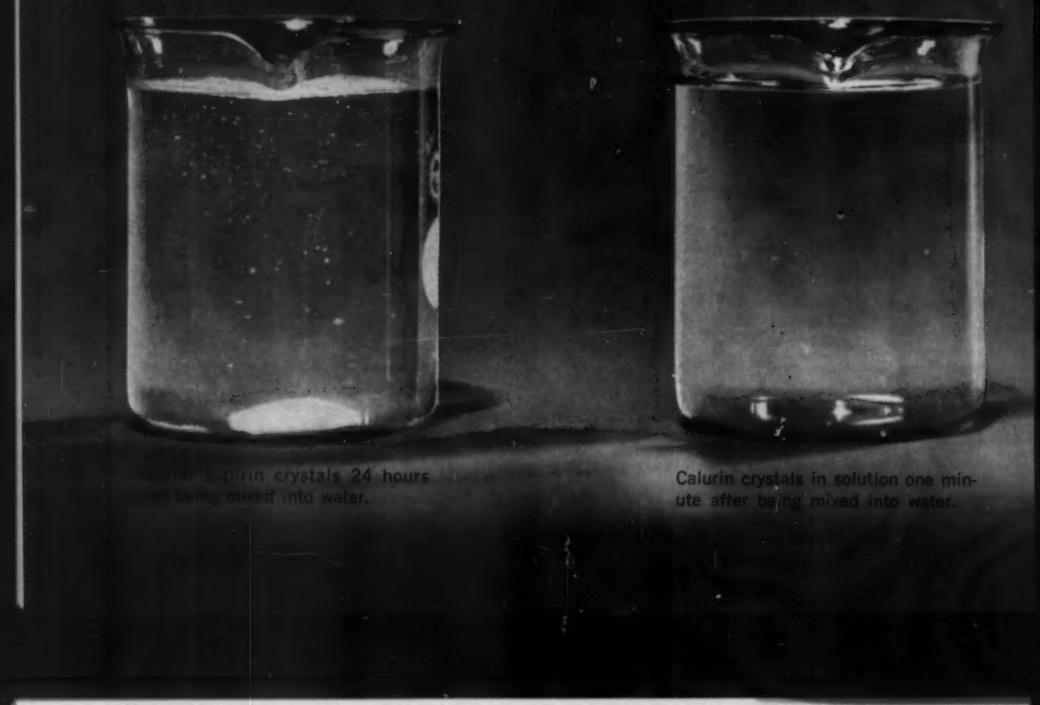

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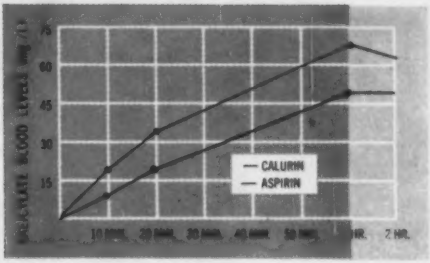

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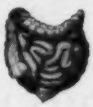
"potent in relaxing the spasm of smooth muscle whether in the G. I., or G. U. tracts, or the gallbladder."[1]

in peptic ulcer — breaks the chain reaction of spasm-pain[2,3]



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Dosage: Mild to moderate cases: initially, 1 or 2 tablets four times daily. Acute or severe cases: 1 to 2 cc. (10-20 mg.) intravenously or intramuscularly every four to six hours up to maximum of 60 mg. in 24 hour period. The higher dosage range is usually required in spasm of the G.U. and biliary tract.

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1. Holbrook, A. A.: Report abstracted in M. Science 4:46 (July 10) 1958. 2. Peiser, U.: Med. Klin. 50:1479 (Sept. 2) 1955. 3. Winter, H.: Medizinische, p. 1206 (Aug. 27) 1955. 4. Berndt, R.: Arzneimittel-Forsch. 5:711 (Dec.) 1955.

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**Over one-million persons past 40 have glaucoma —a major cause of blindness. Incidence increases rapidly with age. Antispasmodics with ocular side effects can induce glaucoma attacks. BENTYL has been proved safe.*

1. Chamberlin, D. T.: Gastroenterology 17:224. 2. Hufford, A. R.: Am. J. Digest. Dis. 19:257. 3. Cholst, M., Goodstein, S., Berens, C. and Cinotti, A.: J.A.M.A. 166:1275, 1958.

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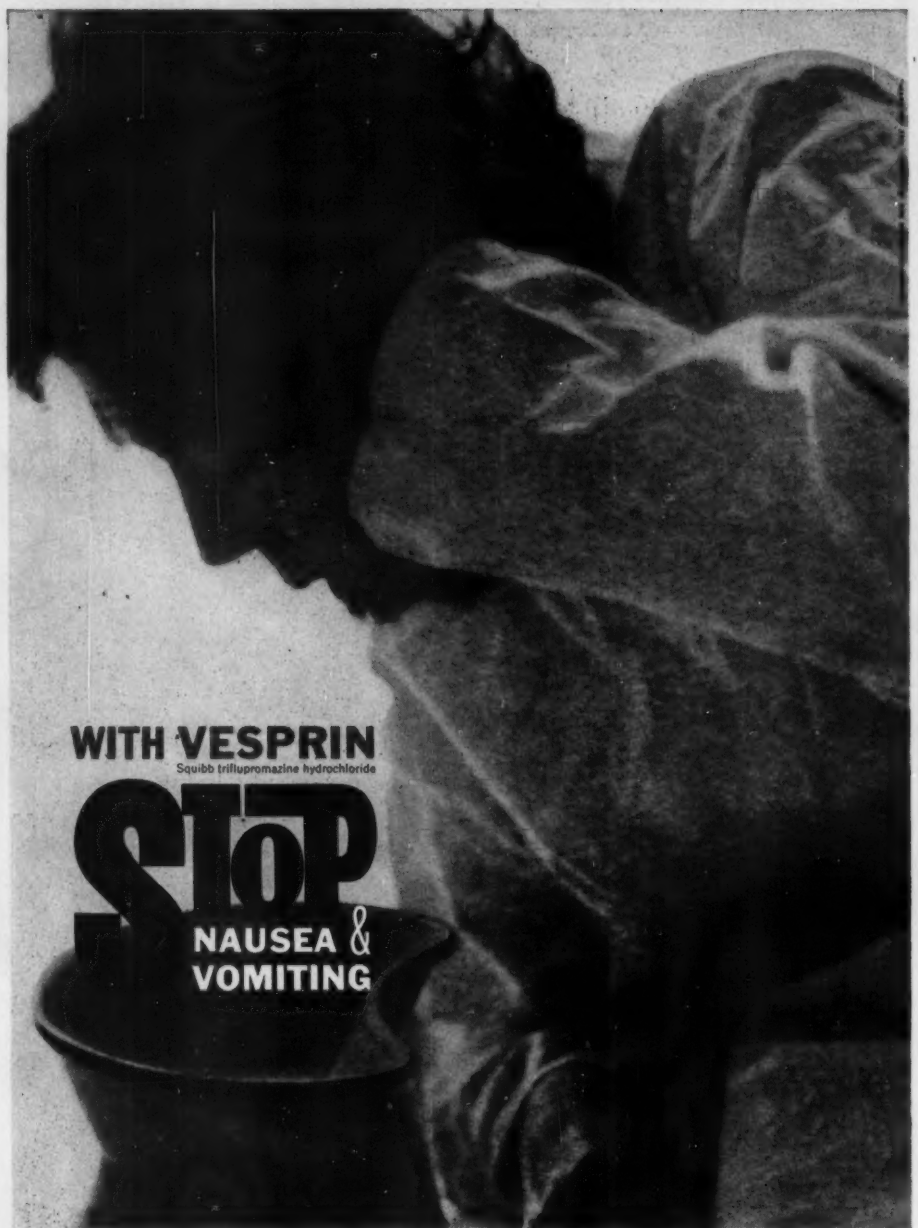

Dosage: Intravenous, 5 to 12 mg. / Intramuscular, 5 to 15 mg. / Oral prophylaxis, 20 to 30 mg. daily / **Supply:** Tablets, 10, 25, and 50 mg., bottles of 50 and 500 / Emulsion, 30-cc. dropper bottles and 120-cc. bottles (10 mg./cc.) / Parenteral Solution, 1-cc. multiple dose vial (20 mg./cc.) / 10-cc. multiple dose vial (10 mg./cc.) / Vesprin Injection Unimatic (15 mg. in 0.75 cc.)

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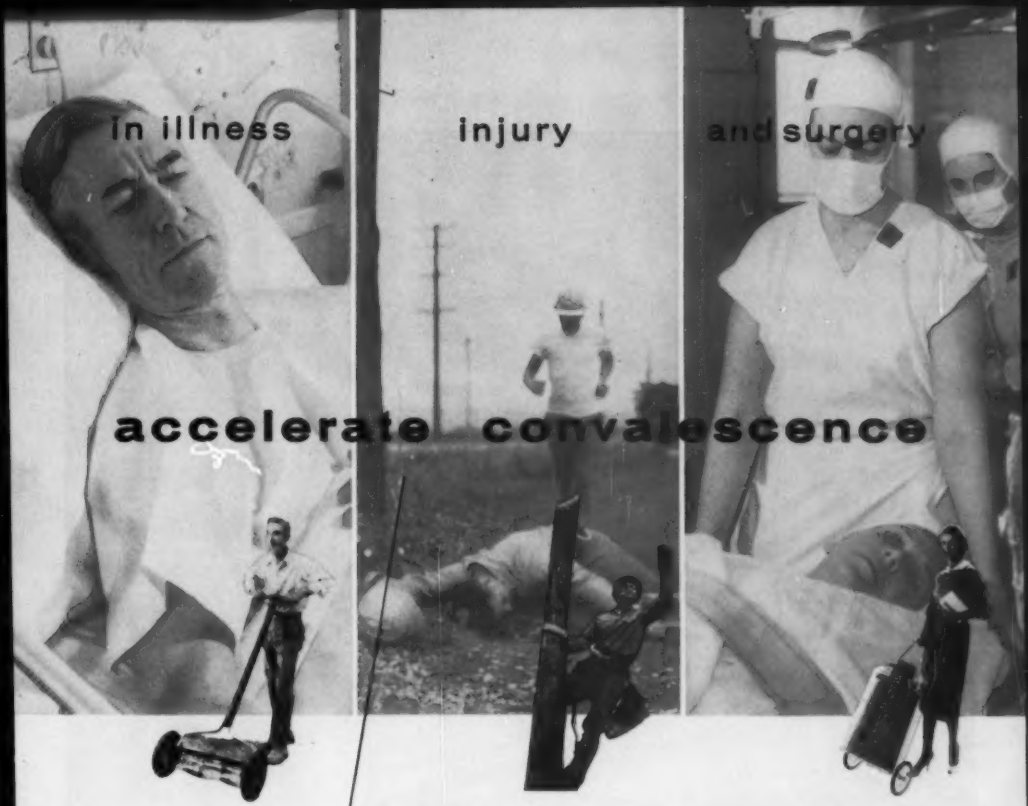

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1. Halpern, S. L.: Ann. New York Acad. Sc. 63: 147-164 (Oct. 28) 1955.

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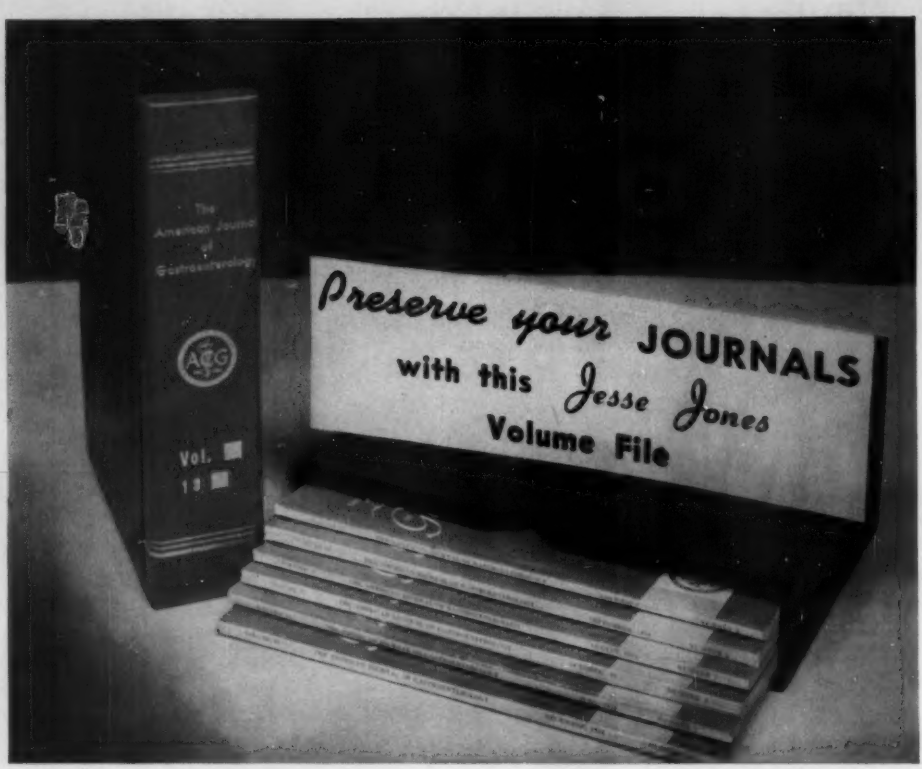

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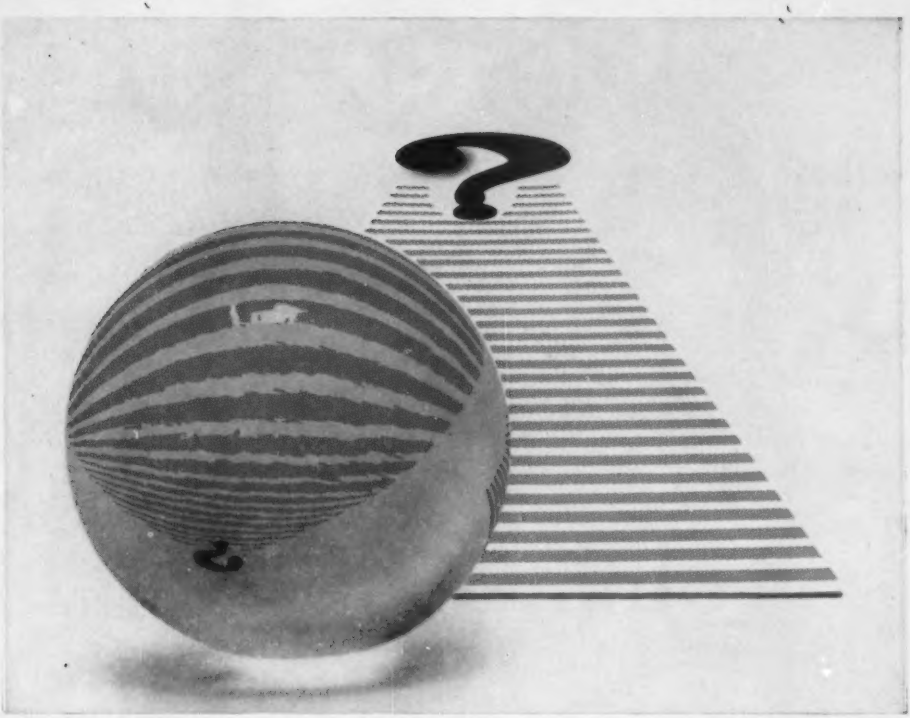

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